PUBLISHED MONTHLY

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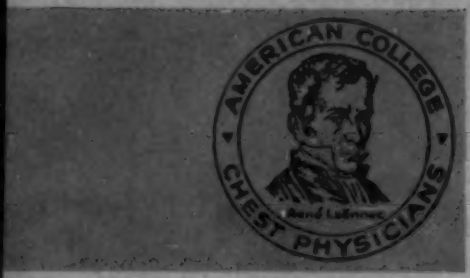
OCTOBER 1959

DISEASES of the CHEST



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- genito-urinary infections
- respiratory tract infections

due to staph or "gram-negatives"

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INJECTION

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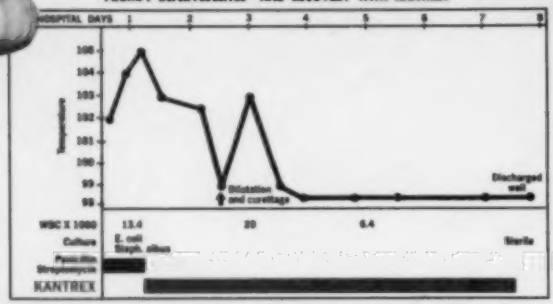


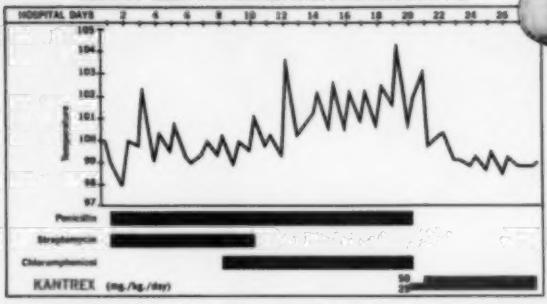
...In gastro-urinary infections due to staph or "gram-negatives"

N. A., a 27-year-old female with postabortal sepsis due to *E. coli* and *Staph. albus* had "prompt defervescence" and recovery with Kantrex after 3 other antibiotics had proved ineffective. No toxic effects were observed.

—Rubenberg, A. M., Kosta, G. M., and Silverstone, F. B.: Annals N.Y. Acad. Sci. 76:341, 1958.

APPENDICEAL ABSCESS

"DRAMATIC" RESULT WITH KANTREX AFTER OTHER ANTIBIOTICS FAIL



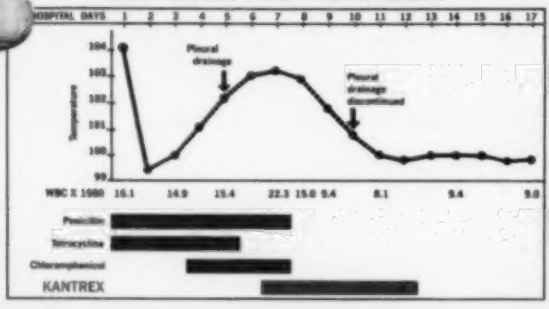
...In skin, soft tissue and post-surgical infections due to staph or "gram-negatives"

J. H. W., 12 year-old boy with appendiceal abscess due to *Staph. aureus*, showed a "clear-cut" and "dramatic" response to Kantrex after 3 other antibiotics had failed. No toxic reaction was noted.

—Yow, E. M., and Mercier, O. T.: Annals N.Y. Acad. Sci. 76:376, 1958.

STAPH PNEUMONIA

KANTREX SUCCESSFUL; 3 OTHER ANTIBIOTICS INEFFECTIVE



...In respiratory tract infections due to staph or "gram-negatives"

T. A., a 4-week-old female infant with pneumonia, pyoderma and septicemia due to *Staph. aureus* showed a prompt beneficial effect and uneventful recovery with Kantrex after 3 other antibiotics had proved unsuccessful. "No serious untoward reactions were observed."

—Riley, H. D., Jr.: Antibiotics Annual 1958-1959, p. 623.

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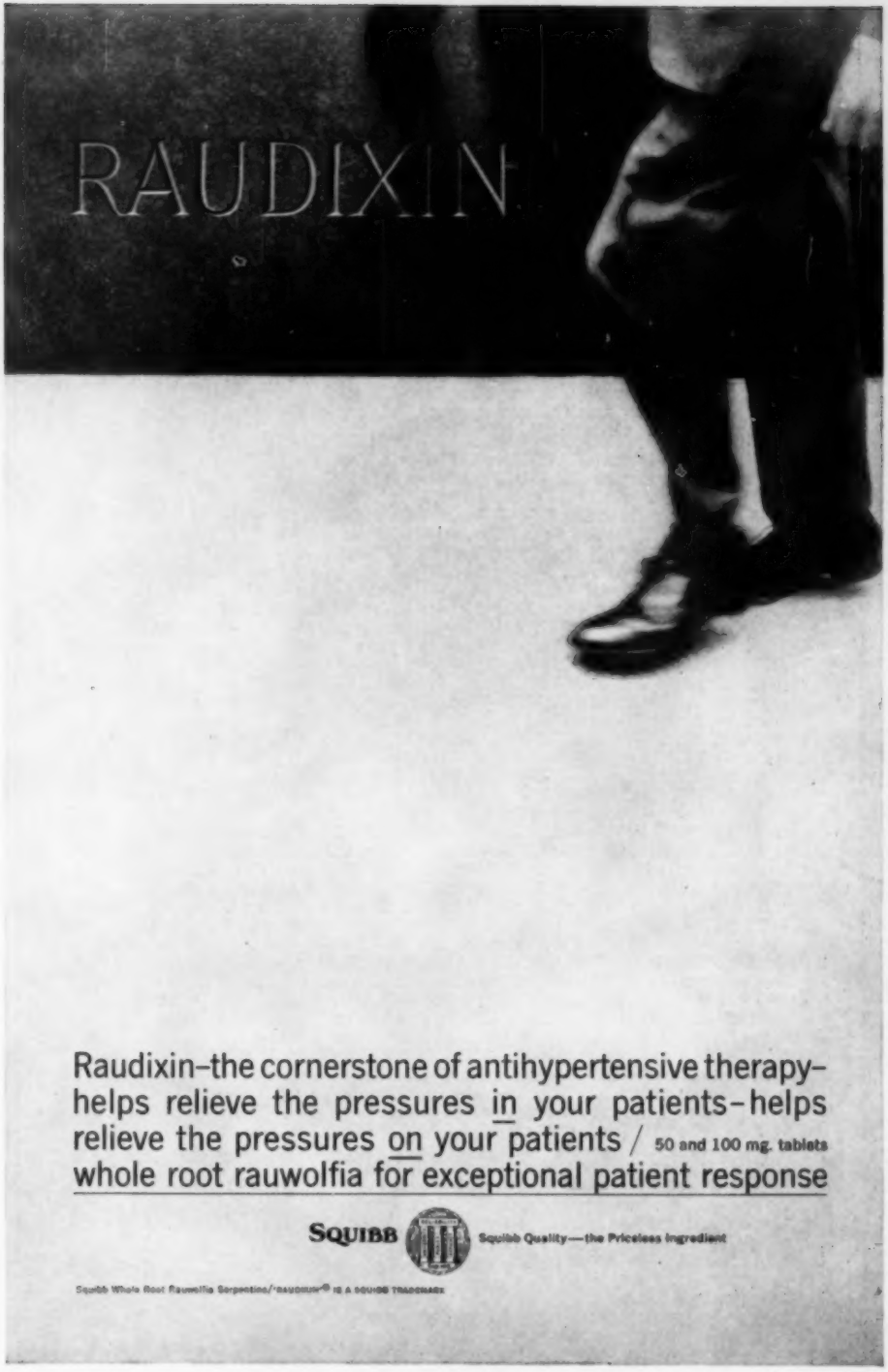

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Krantz, J. C., Jr.: The restless patient—A psychologic and pharmacologic viewpoint. Current M. Digest 25:68, Feb. 1958.

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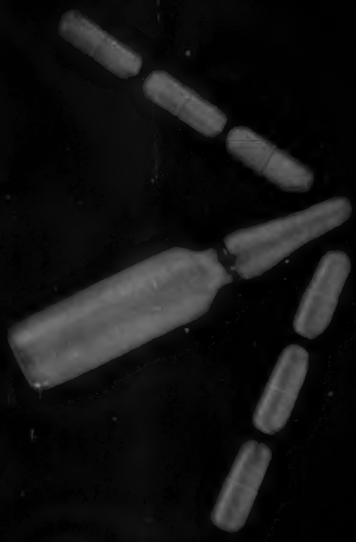

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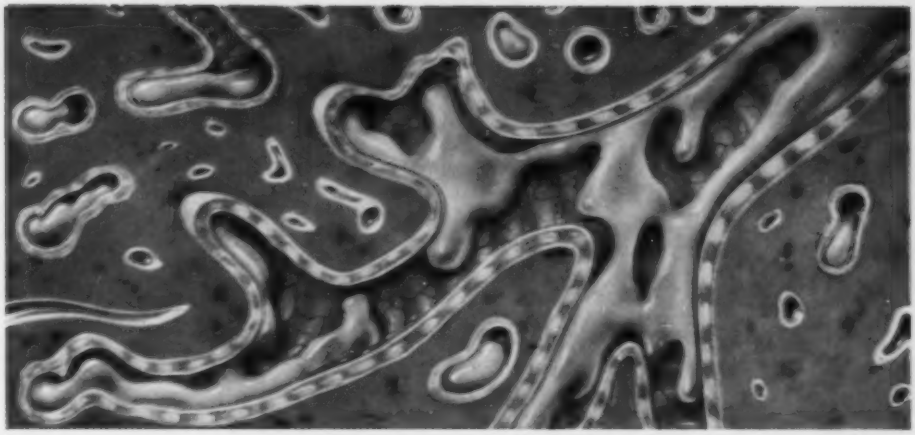

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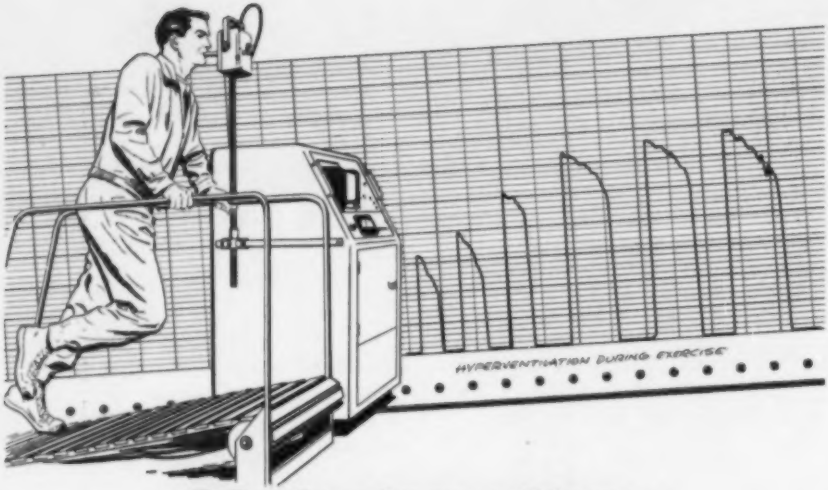

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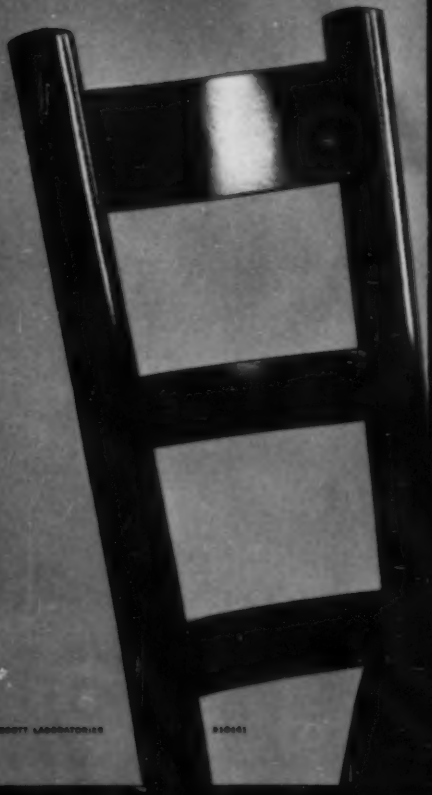

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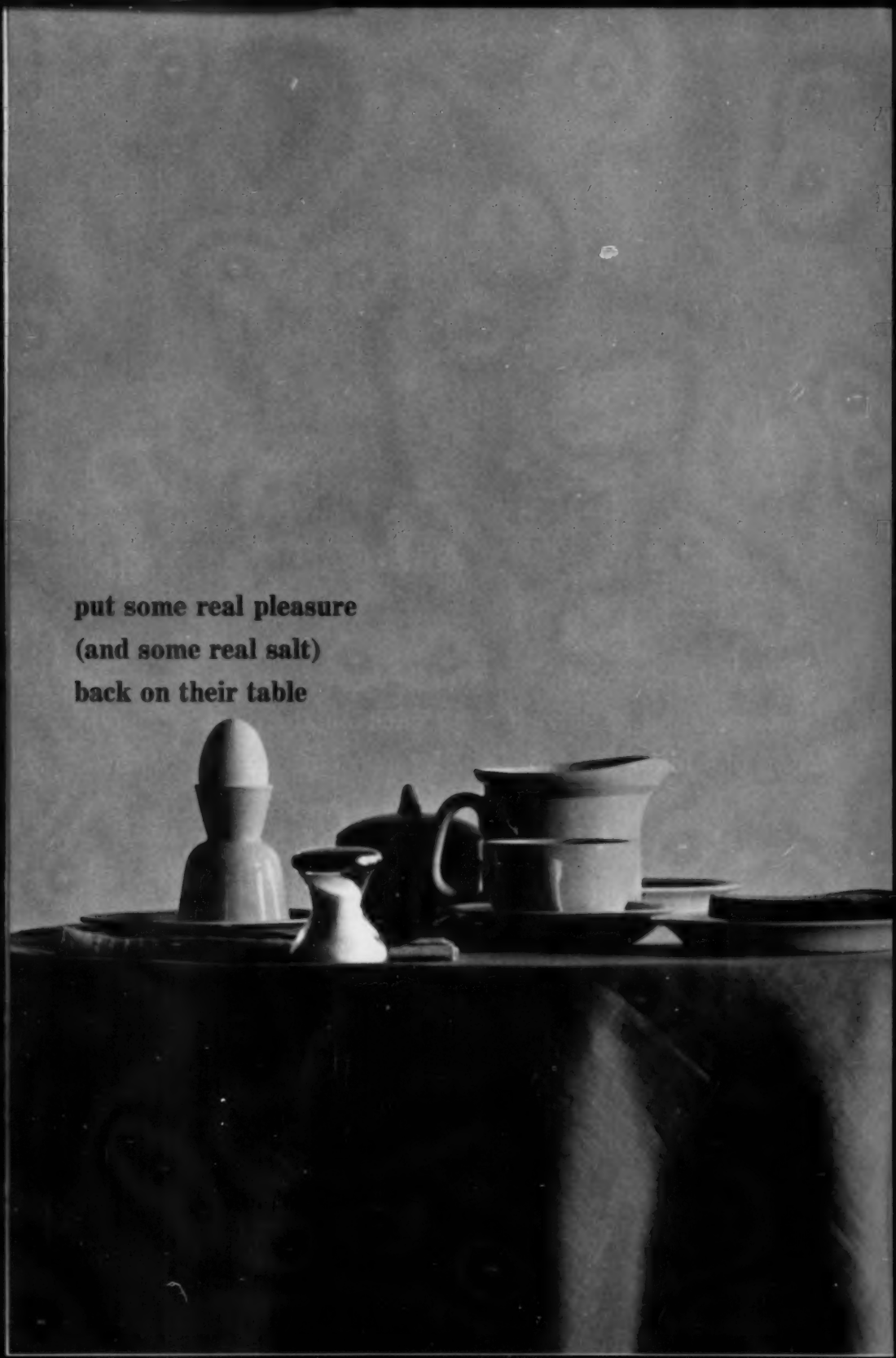
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The desired percentage of concentration is set on a meter—just like the desired temperature. The electronic control unit automatically adjusts the flow of oxygen to maintain the prescribed concentration. This new oxygen concentration control unit, called the O.E.M. AUTOMATIC MECHANAIRE, is perhaps the most important advance in oxygen tent therapy since the tent was invented.

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A sample of the atmosphere under the canopy is constantly being drawn into a continuous oxygen analyzer. Every 15 seconds, the concentration is monitored. The control unit maintains the concentration within a 6% range.

When the monitor finds the concentration below the range, oxygen at 40 liters a minute is flushed into the tent. There is a visual indication that oxygen is flushing into the tent. Oxygen continues to flush into the unit until the concentration is within the preset range. When the monitor discovers this, the flow of oxygen drops to a maintenance flow of 12 liters per minute . . . visually indicated on the control panel. If the oxygen concentration rises above the desired range, maintenance flow is cut off and air is flushed into the tent to bring the concentration down.

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Note that when a lower concentration is desired, it is not achieved merely by shutting off the oxygen flow. On the O.E.M. *AUTOMATIC* MECHANAIRE, an automatic air safety valve starts drawing room air into the tent as soon as the oxygen flow drops below 6 liters per minute. There is no danger of carbon-dioxide build-up because either air or oxygen in substantial quantities is being drawn into the canopy constantly, washing out the carbon-dioxide.

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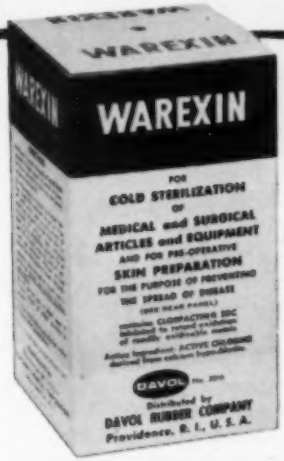

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REFERENCES:

Tentative Methods for the Evaluation of Bactericidal, Sporicidal and Fungicidal Properties of Agents Employed for Chemical Disinfection of Instruments and Heat Labile Goods, A.M.A. Council on Pharmacy and Chemistry, May, 1950.

Lattimer, John K., and Spirito, A. L.: Clorpactin for Tuberculous cystitis: Instrument sterilization. Journ. of Urology, Vol. 73, No. 6, June 1955.

Clowes, Jr., G. H. A., and Neville, W. F.: The Membrane Oxygenator-Extracorporeal Circulation, published by Chas. C. Thomas, Springfield, Illinois in 1958. Page 87.

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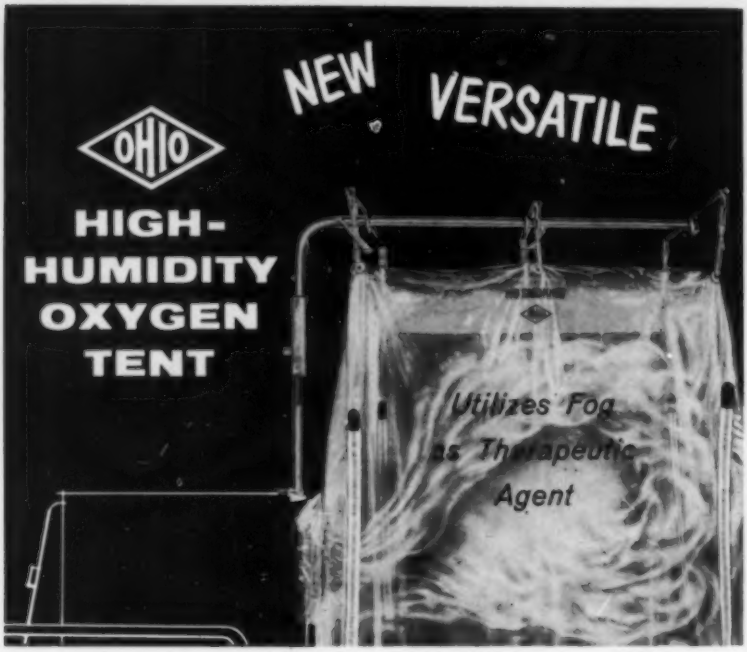

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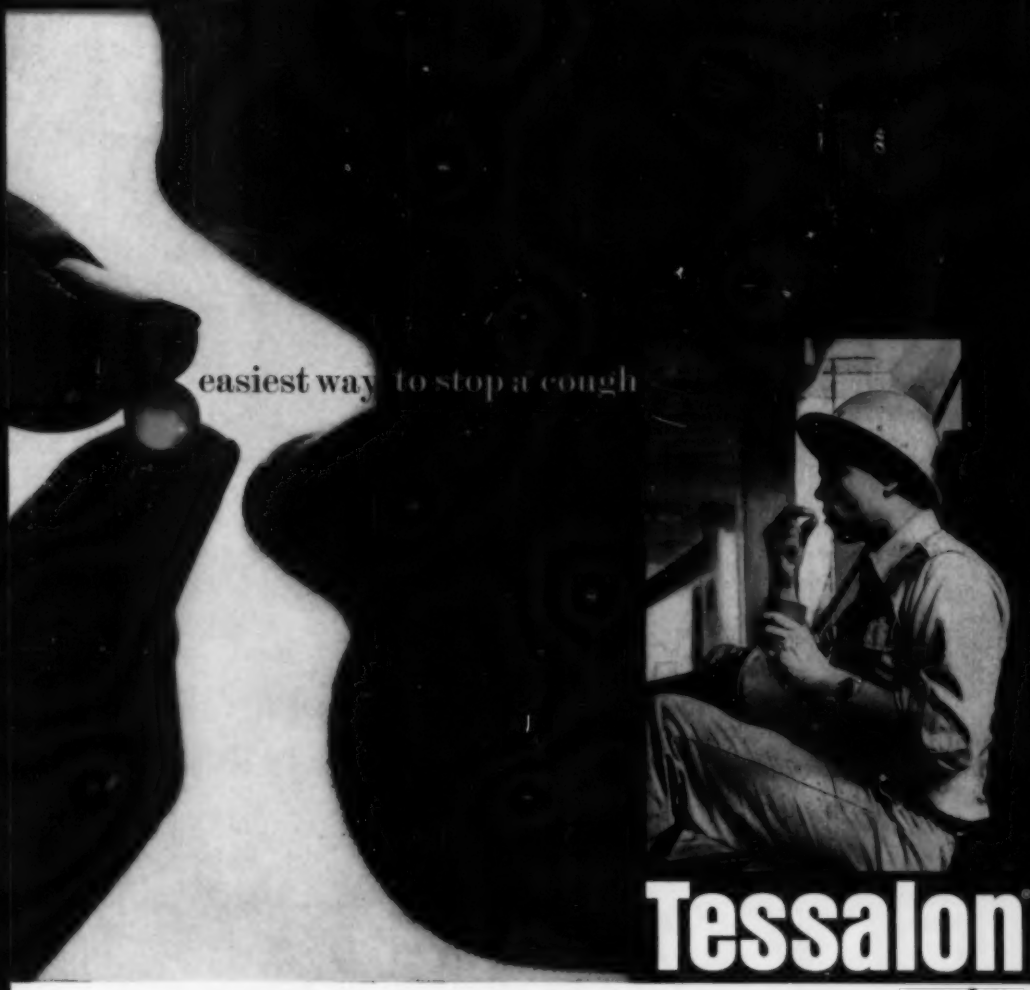

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1. Shane, S. J., Krzyski, T. E., and Copp, S. E.: Canad. M. A. J. 77:600 (Sept. 15) 1957.

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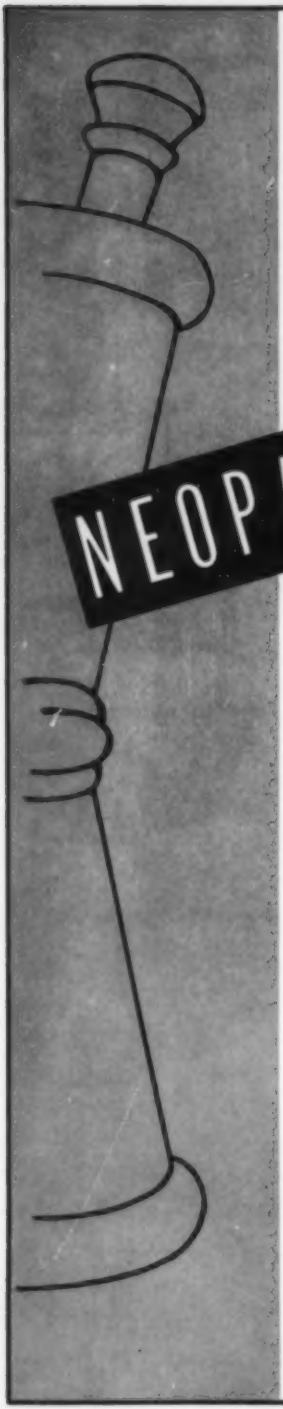

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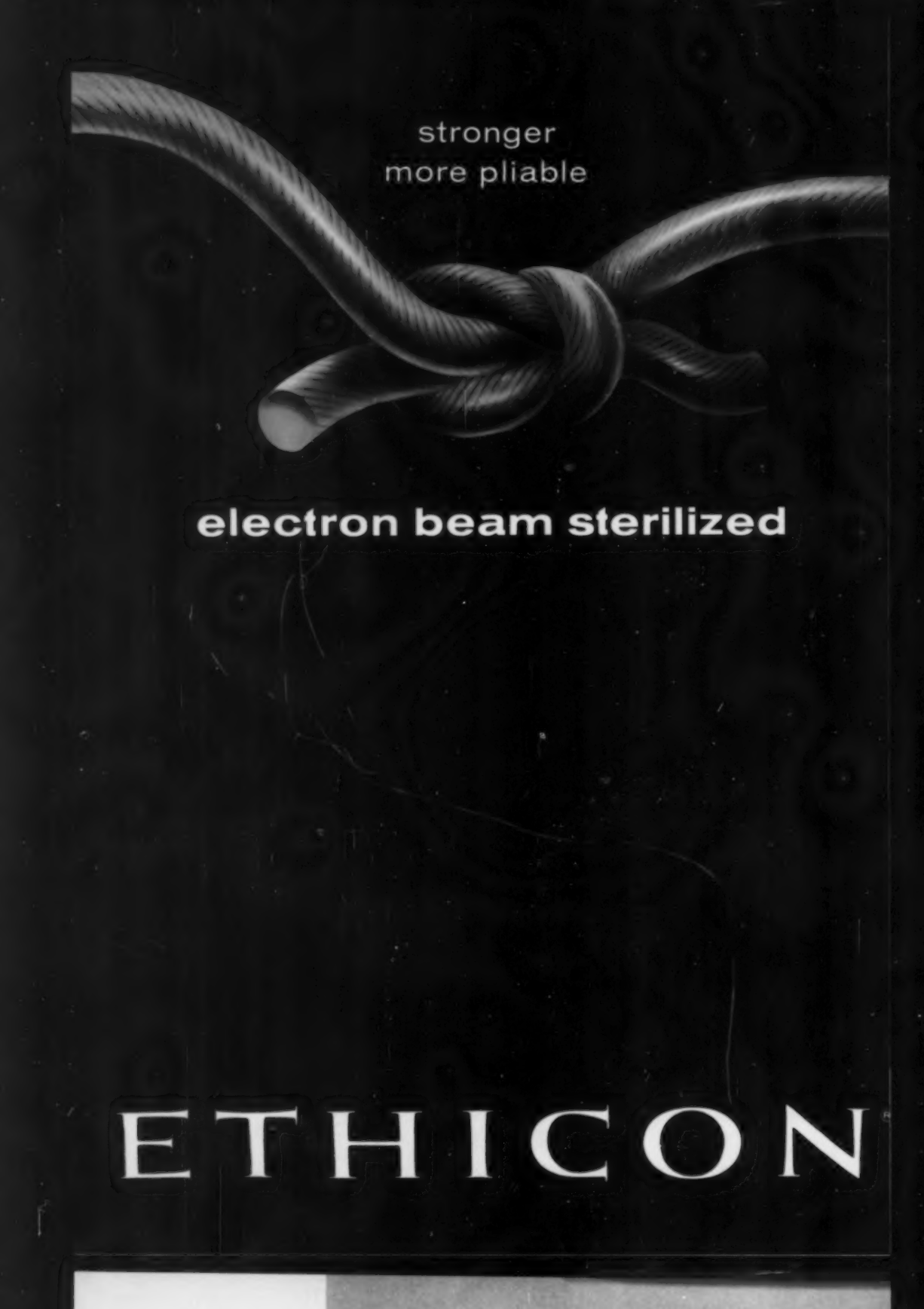
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REFERENCES: 1. Gearren, J.B.: Dis. Nerv. System *20*:66 (Feb.) 1959. 2. Margolis, E.J., et al.: Scientific Exhibit at 12th Clinical Meeting of the American Medical Association, Minneapolis, Dec. 2-5, 1958. 3. Phillips, F.J., and Shoemaker, D.M.: *ibid.* 4. Ayd, F.J., Jr.: Clin. Med. 6:387 (Mar.) 1959. 5. Tedeschi, D.H., et al.: in *Trifluoperazine: Clinical and Pharmacological Aspects*, Philadelphia, Lea & Febiger, 1958, pp. 23-33.

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References: 1. Freyhan, F. A.: Psychopharmacology Digest, Boston, Little, Brown & Co., 1958, p. 7. 2. Ayd, F. J.: The current status of major tranquilizers, in press.

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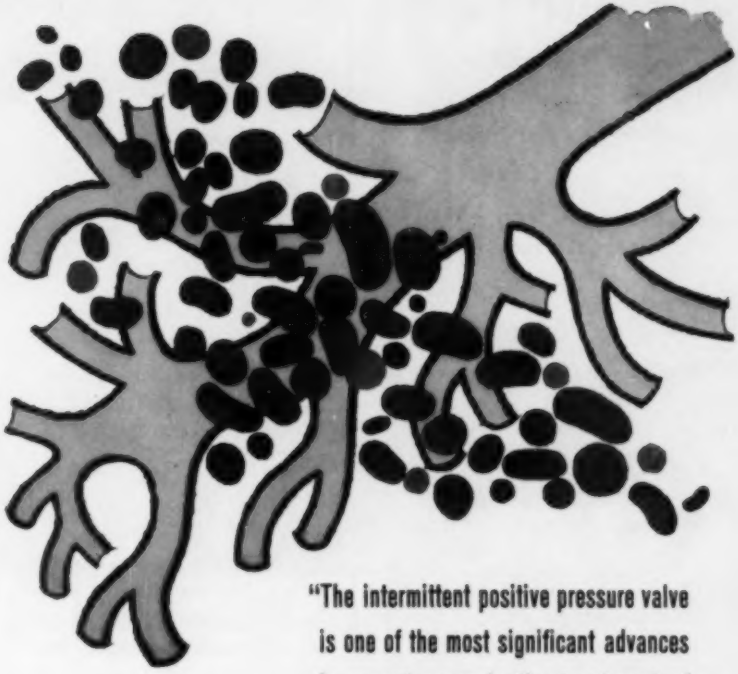

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Homecoming Meeting
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October 14-17, 1959

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American College of
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Dallas, Texas
November 29-30, 1959

POSTGRADUATE COURSES

12th Annual Course on
Diseases of the Chest
New York City
November 9-13, 1959

5th Annual Course on
Diseases of the Chest
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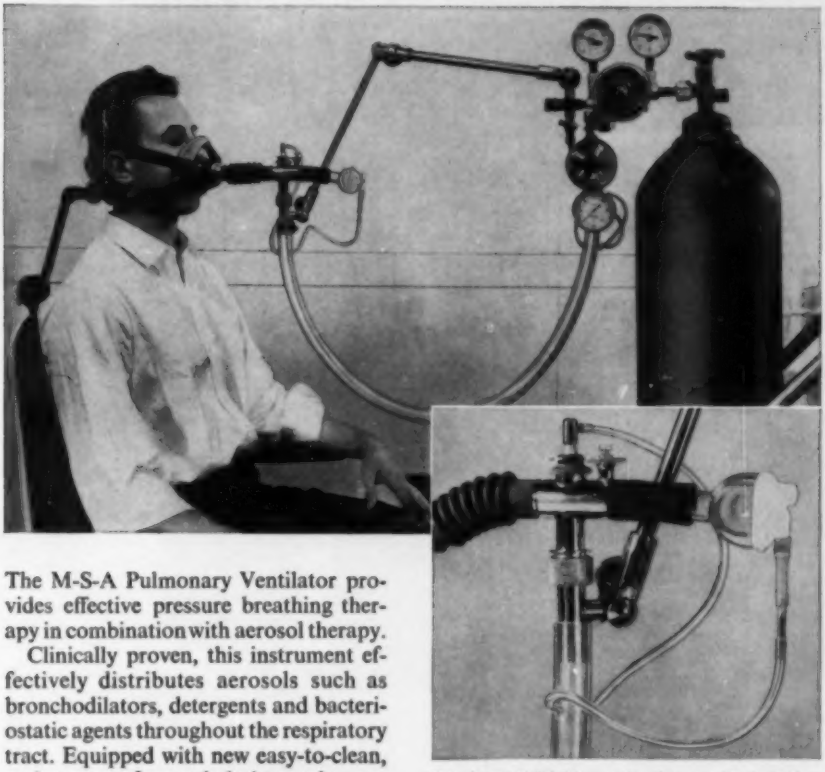

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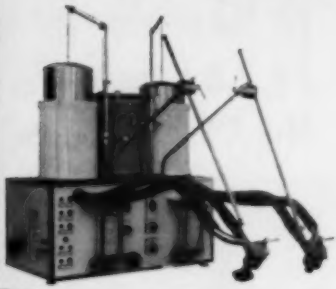

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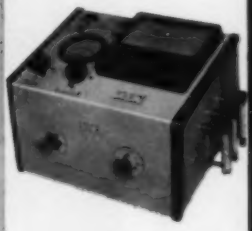

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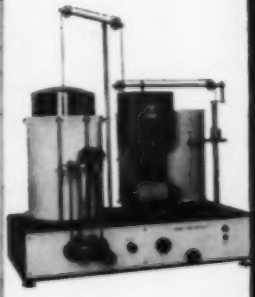

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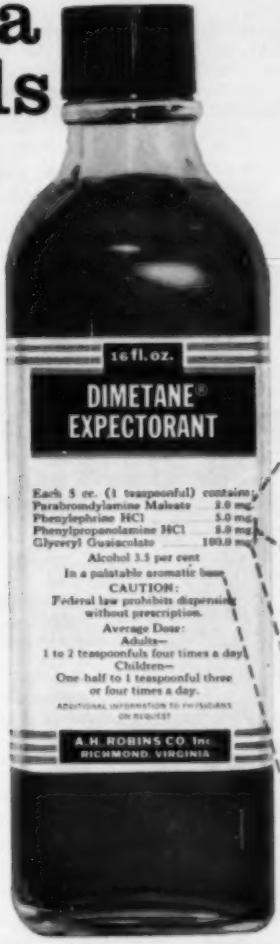

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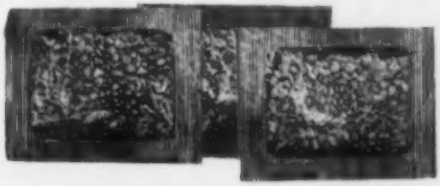

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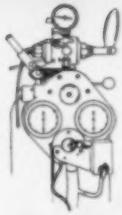

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DISEASES of the CHEST

VOLUME XXXVI OCTOBER, 1959 NUMBER 4

Mediastinoscopy:* A Method for Inspection and Tissue Biopsy in the Superior Mediastinum

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Stockholm, Sweden

For reasons as yet unknown bronchial carcinoma has become a more and more common disease all over the world. Despite increased dissemination of information and better diagnostic methods, such as mass radiography and cytologic investigation, the majority of these patients reach the surgery too late for treatment. In the majority of cases ordinary clinical examining methods, e.g. radiography and bronchoscopy, are sufficient to show that lesions are inoperable. In order to determine if extrathoracic involvement is present, Daniels' method with scalene node biopsy has proved extremely valuable and has gained ever wider acceptance. This method can sometimes be technically difficult, however, and, if it is to be reliable, demands considerable experience, as pointed out by Storey et al. It may even be difficult to decide from which side of the neck the lymph node biopsy specimens should be taken, and sometimes bilateral intervention becomes necessary. Radner has therefore instead recommended biopsy of the paratracheal nodes through incision in the suprasternal notch.

If carcinoma metastases are demonstrated in the lymph nodes of the neck, the majority of surgeons do not take further operative measures. Radical extirpation of the tumor is inconceivable, of course, in these cases, and even a so-called palliative pneumonectomy is surely technically impossible in many of them because of involvement of other organs in the mediastinum. In some clinics cardio-angiography is also used to preclude the possibility of tumor involvement of the central vessels. Notwithstanding that, accordingly, a great deal of effort is expended before operation in most institutions to evaluate the operability, we find in extensive series of cases that from 30 to 45 per cent of all patients undergoing thoracotomy for bronchial carcinoma are inoperable. In a series of 767 cases of bronchial carcinoma of different types described by Kirklin et al. (1955), thoracotomy was not done in 52 per cent, resection with a view to cure was possible in only 24 per cent and resection for palliation in 5 per cent. In the remaining 19 per cent of the cases the tumor proved unresectable at operation, i.e. in almost 40 per cent of those subjected to thoracotomy. Even if an exploratory thoracotomy is not today considered a risky intervention, we should bear in mind that these poor patients lose, just through the operation, one or two of the best months they have left

*From the Clinic of Thoracic Surgery, Karolinska Sjukhuset.

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to live. Many never regain their strength, and, because they take up hospital beds over long periods, prevent the admission of other patients in operable condition. It has been contended that from the psychologic point of view for the patient the performance of an exploratory thoracotomy may be justified in cases where it has not been possible to determine the operability with certainty preoperatively. Moreover, there are, to be sure, also isolated cases reported in which a so-called palliative operation on a patient clinically considered inoperable has resulted in a surprisingly long survival. These are great exceptions, however, and cannot justify thoracotomy in all cases of clinically inoperable bronchial carcinoma.

In many borderline cases our ordinary clinical methods of examination are not able to give sufficient information. Even if scalene node biopsy seems to have precluded the possibility of extrathoracic spread, a local tumor involvement in the mediastinum can make radical intervention impossible. It seems also as if the most common type of tumor, the squamous cell carcinoma, can cause extensive intrathoracic changes before any more peripheral involvement occurs. For instance, Shefts et al. writes: "It is considered noteworthy that of the 13 carcinomatous scalene nodes the tumors in nine were undifferentiated in type and in four patients were adenocarcinoma. No squamous cell carcinoma was found in the nodes. In the seven patients with uninvolved scalene nodes who had thoracotomies

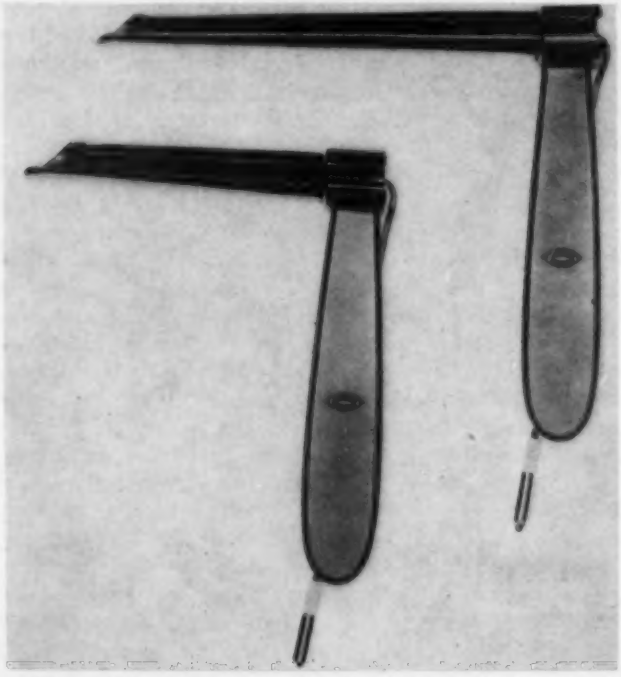

FIGURE 1: Photograph of two scopes for investigation of the mediastinum. The longer and thinner one is specially built for inspection of the carina region.*

*The instruments are made by A. B. Stille-Werner, Stockholm, 4, Sweden.

(two had mediastinal involvement), all of the tumors were squamous cell carcinoma." We have therefore sought a procedure that is simpler for the patient than thoracotomy to determine the extent to which a bronchoscopically demonstrated widening and fixation of the carina or a radiographically visualized broadening of the superior mediastinum is caused by metastatic carcinoma. Harken et al. (1954) described a cervicomediastinal exploration in conjunction with Daniels' operation. Notwithstanding that the writers themselves considered the procedure useful and reported no serious complication, the method does not appear to have been imitated. The few complications described were ruptures on the thoracic duct and the big veins in the neck and two cases of pneumothorax. Their operation is performed under local anesthesia with introduction of a laryngoscope through the lateral incision in the neck. In some cases it was necessary to apply the procedure bilaterally. As the main objection to the described method seems to be the great risk involved in the procedure, we have attempted in different ways to make is "safer" and less distressing to the patient.

Method

The shortest approach to the superior mediastinum is through an incision in the suprasternal notch. With the patient's head tilted slightly backwards and rotated to the left, a 3 to 4 cm long incision is made transversely in the skin. The soft tissues are then divided along the midline down to the anterior wall of the trachea. In this manner bilateral inter-

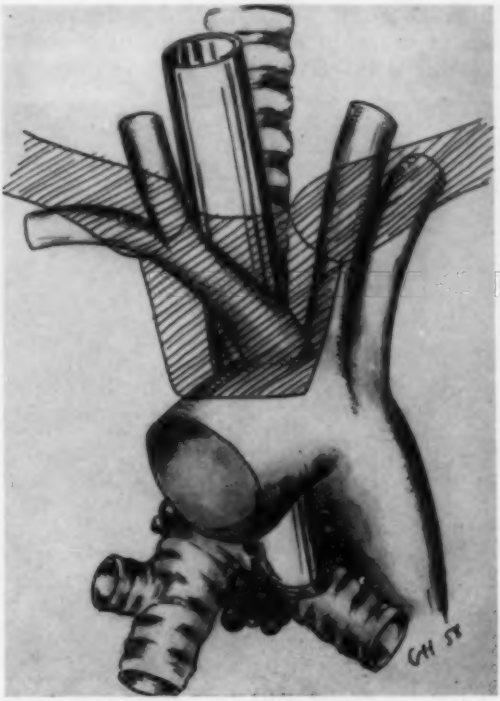

FIGURE 2: Diagram showing the scope introduced through an incision in the suprasternal notch.

vention becomes unnecessary and the risk of injuring the large vessels in the neck and the pleura is avoided. In addition, the operation is performed under intubation anesthesia to preclude coughing and to eliminate the risk of mediastinal emphysema, which might quite conceivably occur if the mediastinum is opened and the trachea should happen to be compressed during the investigation so that an increased negative pressure is produced in the thorax. Vena thyreoida ima is often ligated. In the majority of cases blunt dissection down along the trachea posterior to the innominate artery and aortic arch can then be performed with the finger. Just behind the innominate artery a number of streaks of firmer fascia invest the trachea. Otherwise, in normal cases, the tissue here is very loose and it is possible to expose the entire trachea down to the bifurcation. Larger lymph nodes are then easy to palpate and can sometimes even be enucleated with the finger. With blunt dissection the risk of injuring the recurrent nerve seems to be extremely slight. No such damage has occurred in any of our cases. A specially designed instrument (Figs. 1 and 2), most closely resembling a children's esophagoschope with a slit in the side, is then introduced into the passage opened along the trachea with the finger. With a blunt-tipped aspirator and a forceps with an angled grip it is possible with visual help to dissect still farther down and to excise specimens of suspected nodes. If there are no pathologic adhesions, the nodes in the carina angle are easily accessible. They are often distinguishable from the surrounding tissues by their black color.

Thus far we have used the method mainly in cases of verified bronchial carcinoma with radiologically demonstrated increases in the breadth of the mediastinum in order to determine the nature of the increase in breadth and to estimate the extent to which the tumor involves adjacent

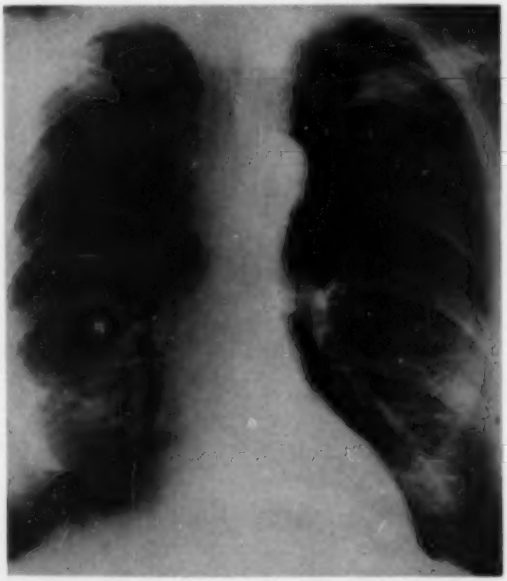

FIGURE 3: Carcinoma in the right main bronchus with atelectasis of the middle lobe and metastases in the paratracheal lymph nodes on the right side. A silver clip indicates where the biopsy specimen was excised during mediastinoscopy.

organs. It has already been possible a number of times, particularly in cases of squamous cell carcinoma, to palpate large, hard tumor metastases, fastly adherent to surrounding tissues, immediately below the suprasternal notch in the absence of any demonstrable nodes whatsoever in the neck. In this way many patients have been spared thoracotomy. After application of sulfa-penicillin powder in the wound, the incision is closed primarily, and the patient is able to leave the hospital the next day. The patient's only discomfort is a slight smarting in the throat persisting a day or two, probably due to the intubation. Since we started applying the method in the middle of 1957 it has been administered to over 100 patients. In no case has a complication arisen. The bleeding after excision of the biopsy specimens or enucleation has always been minimal and stopped spontaneously. Once or twice a silver clip was applied to some minor vessel, but for the most part these were used only to permit visualization on a subsequent radiogram of the site of specimen excision.

Case Reports

Case 1: G. B. The patient, a man aged 63 years, had good general condition. Six years earlier he had had a relatively slight cardiac infarction but had otherwise been healthy previously. During the past three months he reported increasing coughing and repeatedly observing blood mixed in his sputum.

X-ray films examination (Fig. 3) showed atelectasis of the middle lobe and fluid basally in the right pleural space. In addition there was an increase in the breadth of the mediastinum on the right side with a slight impression of the trachea most inferiorly.

Bronchoscopy also revealed an impression of the right tracheal wall but a normal carina, which was comparatively movable. One centimeter inferior to the origin of the bronchus to the upper lobe the main bronchus was almost completely filled by a tumor. Biopsy showed it to be a squamous cell carcinoma. From the bronchoscopic point of view the tumor was considered operable.

Mediastinoscopy was done to permit more detailed investigation of the mediastinum. After an incision in the suprasternal notch, we dissected down along the anterior wall of the trachea. Immediately below the thoracic aperture up to plum-sized, hard

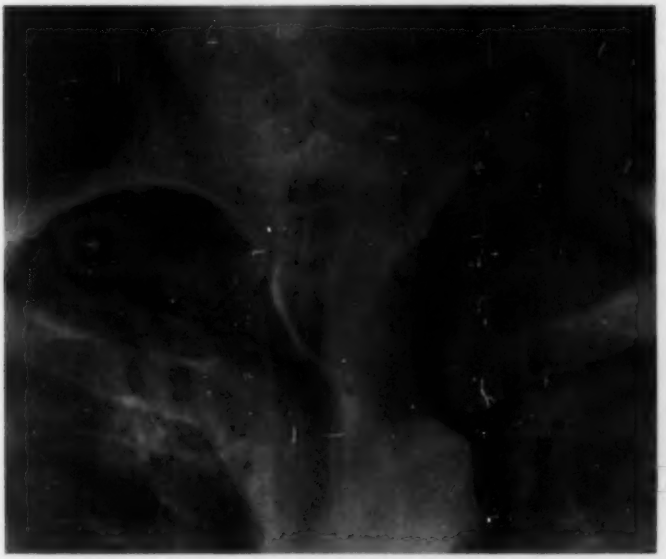

FIGURE 4: The x-ray shows a hen's egg-sized, expanding lesion to the left in the superior mediastinum in a patient with a verified carcinoma in the bronchus to the left lower lobe.

nodes were palpated on the right side. The uppermost could be freed from the trachea, but farther down they were firmly fixed and growing directly over onto the trachea. Biopsy revealed carcinoma metastases.

Because of the large glandular metastases the tumor was considered inoperable, and it was not necessary to perform an exploratory thoracotomy.

Case 2: S. M. The patient, a 55-year-old man, presented a history of periodic gallstone trouble for 10 years and mild diabetes for seven. The last six months he had been coughing with slight hemoptysis. In connection with an operation for gallstones a change was visualized radiographically in the left lung. The first x-ray showed a fluid level at the height of the apical segment of the lower lobe. Puncture was done, and a half liter of pus containing staphylococci was aspirated. A new x-ray film revealed a tangerine-sized tumor in the left lower lobe, which was completely atelectatic. In addition, in the upper part of the mediastinum on the left side an expanding lesion the size of a large hen's egg was observed displacing the trachea and esophagus to the right (Fig. 4). The diaphragm on the left was almost totally immobile, giving rise to suspicion of a malignant tumor with large glandular metastases in the mediastinum.

Bronchoscopy showed a tumor filling the entire bronchus to the left lower lobe. Biopsy showed it to be a squamous cell carcinoma. No nodes in the neck or enlargement of the thyroid were palpable.

The operability of the tumor was questioned, but to permit more detailed investigation of the nature of the mediastinal change mediastinoscopy was done. After exposure of the trachea, dissection with the finger anterior to and to the right of the trachea down to the carina tract was easily carried out. On the left side it was possible to dissect free a hard, small-lobed tumor the size of a hen's egg, which appeared to have no connection with the thyroid superiorly. It was removed as was a hazelnut-sized, lymph node-like formation lying completely free farther down posterior to the aortic arch. Microscopic investigation showed both extirpated tumors to be benign thyroid adenoma. No carcinoma metastases were found.

Thoracotomy subsequently revealed a relatively well-delimited tumor in the left lower lobe without any visible metastases in the lymph nodes. Pneumonectomy was performed. The postoperative course was normal.

Case 3: H. G. The patient, a woman aged 71 years, had previously been in general good health. During the last eight months she had been losing weight and during the last six months had had recurrent periods of fever and hemoptysis.

Radiography revealed a tumor-like change with atelectasis in the entire left lower lobe, marked enlargement of the left hilar region and fluid basally in the pleural cavity.

Bronchoscopy showed a somewhat wide carina, which was markedly fixed. Only 2 cm. below the carina the left main bronchus was almost completely filled by a tumor. The region felt hard. From the bronchoscopic view-point the tumor was adjudged inoperable. Biopsy showed it to be squamous cell carcinoma.

For her age the patient's spirometry values were good, and she herself wished to undergo operation. For this reason as further preliminary examination mediastinoscopy was done. This showed the trachea to be easily movable, and no pathologic node could be palpated in the tracheo-bronchial angles. It was also easy to dissect down past the carina region without encountering any larger nodes. A silver clip was applied to the deepest point (Figs. 5 and 6).

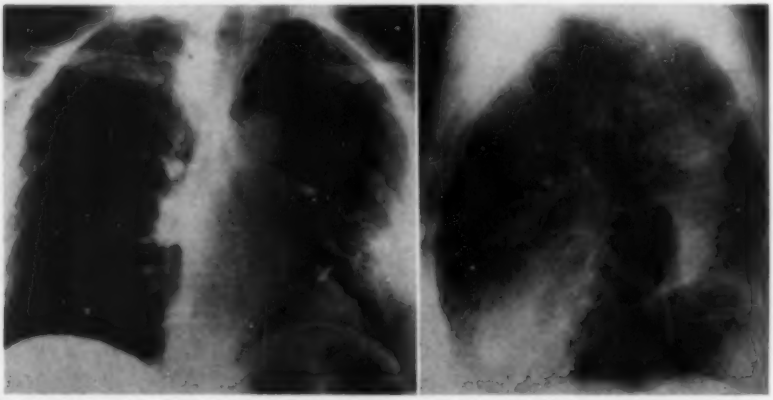

FIGURE 5 and 6: Frontal and lateral x-ray views of a patient with a tumor in the left main bronchus and with atelectasis of the lower lobe and broadening of the hilus. A silver clip indicates the lowest point reached during mediastinoscopy.

FIGURE 7: X-ray of 57-year-old man with a slight increase in the breadth of the superior mediastinum and a narrow trachea, interpreted as due to compression.

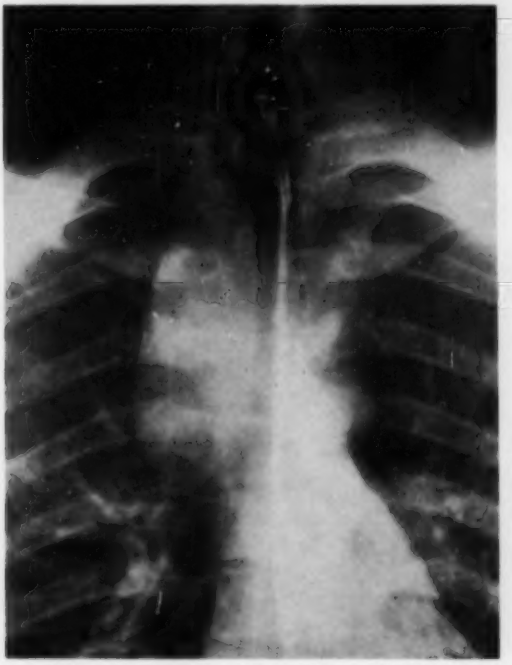

FIGURE 8: X-ray of 20-year-old man with a thin-walled, benign cyst to the right in the mediastinum.

She was thereafter advised to submit to operation. The tumor then proved to be comparatively large but well limited to the lung, and no node could be demonstrated in the carina angle or out along the trachea. The postoperative course was normal.

In this case the tumor was first adjudged inoperable, but after mediastinoscopy thoracotomy was considered indicated despite the relatively advanced age of the patient.

Case 4: L. G. The patient was a 57-year-old, rather corpulent man. During his younger years he had been generally healthy. During the last 10 years he had observed increased shortness of breath on exertion. He had sought medical advice several times but no pulmonary or cardiac lesions had been found. Bronchial asthma had been suspected.

X-ray film examination in January 1958 revealed a slight increase in the breadth of the superior mediastinum with an extended compression of the trachea, in which the lumen was estimated to be about half the normal width (Fig. 7).

Bronchoscopy showed an extended narrowing of the trachea, which was interpreted as an impression from the right. Bronchoscope No. 9 could not be introduced, but No. 7 passed relatively easily, and normal conditions could be visualized below the carina.

In an attempt to determine the nature of the tracheal compressions mediastinoscopy was performed. It was surprising to find that this revealed fully normal conditions in the mediastinum with the trachea easily movable. On the other hand, throughout its entire length, from immediately below the larynx to the bifurcation, the trachea proved to be considerably narrower than normally, with a maximum external diameter of 12 mm. It appeared otherwise normal.

Apparently this case is to be interpreted as a probably congenital hypoplasia of the trachea, which gave increasing symptoms with increasing age and body weight. The possibility of a suspected mediastinal tumor could be entirely precluded without thoracotomy.

Case 5: G. K. The patient, a man aged 20 years, had always been in good general health. At the age of 12 years mass radiography revealed an increased density within the right part of the mediastinum. Radiographic control examination three years later showed no increase. The change, approximately unchanged, was again visualized

FIGURE 9: Photograph of a 52-year-old man with a plum-sized tumor in the left upper lobe and increased density paratracheally on the right side.

during the patient's military service after another five years. In the x-ray films (Fig. 8) at this time an oblong shadow with a smooth, slightly rounded contour could be visualized within the upper part of the mediastinum on the right side. To the left this formation was delimited by the trachea, which was displaced somewhat to the left. The change extended from the superior thoracic aperture down to the bronchus of the right upper lobe. Tomography showed that it was free from the aorta. Intrathoracic struma was suspected, but the scintigram tracer iodine was normal.

At mediastinoscopy no tumor-like change could be palpated, but immediately to the right of the trachea a paper-thin, cystic formation could be seen in the mediastinoscope. On puncture abundant water-clear, yellow fluid was obtained. Biopsy of the wall of the cyst was done. Malignancy could be precluded microscopically, but the origin of the cyst could not be determined. Thoracotomy was not done, but the patient was placed under continued observation.

Case 6: The patient was a 52-year-old man with previous good health. During the last three months he had complained of hoarseness, fatigue and increasing headache.

Radiography (Fig. 9) revealed a plum-sized tumor with partial atelectasis in the anterior part of the left upper lobe. The left hilar region was enlarged and there was increased density paratracheally even on the right side.

Bronchoscopy showed left-sided paralysis of the recurrent nerve but otherwise largely normal conditions. No tumor could be visualized.

At mediastinoscopy large, hard, partially fixed nodes were encountered high up to the right of the trachea. No node could be palpated on the left side. Biopsy showed it to be squamous cell carcinoma.

The tumor was considered inoperable, and the patient died later with brain metastases.

This case demonstrates how it is sometimes possible to obtain a histologic diagnosis with mediastinoscopy when bronchoscopy is unsuccessful. It is also interesting as it shows that even upper lobe tumors on the left side can give metastases on the other side of the trachea although it is generally believed that only left-sided tumors of the lower lobe can give crossed metastases.

In addition to application in cases of the type described here the method has often been used for test excision of nodes in systemic diseases of various kinds. It has proved particularly valuable in sarcoidosis, where it has always been possible to enucleate large nodes for microscopic examination, several times even in cases where scalene node biopsy has not been successful despite having been performed by an experienced surgeon. Other mediastinal changes that have been excised for biopsy are lymphosarcoma, Hodgkin's disease and lymph node metastases from gastric and mammary carcinoma. As in the case of tracheal hypoplasia described, the method has also been used for inspection in a case of extensive amyloidosis in the tracheal wall. In cases of benign tracheal tumors the method would seem valuable for determination of the extratracheal extent and in the planning of continued therapy.

In analogy with all other procedures, the reliability of the method increases and the risks decrease with the increasing experience of the examiner. The writer recommends several preliminary experiments on cadavers and advises test excision of only easily accessible nodes in the first cases. Together with scalene node biopsy, which it partially replaces, the method would seem to have a certain value in cases presenting unexplained mediastinal changes and especially in the cases in which it is possible to spare the patient an exploratory thoracotomy.

SUMMARY

A method is described by which through a short incision in the suprasternal notch it is possible to dissect down along the whole length of the trachea and to palpate with a finger the immediately surrounding tissues. A specially designed instrument, resembling a children's esophagoscope, is introduced into the passage thus dissected, and specimens from pathologic changes are excised or the tissues punctured with visual aid. The operation, which is performed under intubation anesthesia, has been used in over 100 cases without a complication.

RESUMEN

Se describe un procedimiento por el cual, mediante una incisión arriba de la horquilla esternal, permite disecar hacia abajo a lo largo de toda la tráquea y palpar con el dedo los tejidos circundantes. Se introduce un instrumento ideado especialmente y semejante a un esofagoscopio para niños, y a través de este túnel así disecado, se pueden tomar especímenes patológicos o se pueden hacer punciones de las partes alteradas bajo el control visual. La operación que se lleva a cabo bajo anestesia por intubación, se ha hecho en más de 100 casos sin complicaciones.

RESUME

L'auteur décrit une méthode selon laquelle, par une courte incision sur l'échancrure suprasternale, il est possible de disséquer le long de la trachée et de palper avec

un doigt les tissus immédiatement avoisinants. Un instrument spécialement conçu, ressemblant à un oesophagoscope pour enfant, est introduit alors dans la tranche de dissection: des fragments des éléments pathologiques sont prélevés ou les lésions sont ponctionnées sous contrôle de la vue. L'opération qui est pratiquée avec anesthésie par intubation a été utilisée dans plus de 100 cas sans complication.

ZUSAMMENFASSUNG

Es wird eine Methode beschrieben, mit deren Hilfe es durch eine kleine Inzision in der Supraclavikulargrube möglich ist, entlang der ganzen Ausdehnung der Luftröhre zu präparieren und mit dem Finger die unmittelbar anliegenden Gewebe zu palpieren. Man führt ein eigens hierfür entworfenes Instrument, das einem Oesophagoskop für Kinder ähnlich sieht, in den vorher präparierten Gang ein und exzidiert pathologisch-veränderte Gewebsstücke oder punktiert unter Sicht des Auges. Die Operation wird in Intubationsnarkose durchgeführt und gelangte in über 100 Fällen ohne Komplikation zur Anwendung.

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Bronchogenic Cysts in Patients Presumed to Have Pulmonary Tuberculosis*

NEIL C. ANDREWS, M.D., F.C.C.P., PHILIP C. PRATT, M.D.
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Bronchogenic cysts have long been recognized as occurring in either the lung or mediastinum.[1-3] Often these are fluid-filled lesions which appear as masses easily confused with malignant or benign neoplasms. Many of the intrapulmonary lesions have come to clinical attention because of infection.[4-6] The need has been suggested of differentiating bronchogenic cysts from blebs, abscesses, bronchiectasis, spontaneous pneumothorax[7] or empyema.[8] As an air-filled annular intrapulmonary lesion, bronchogenic cyst may be confused with the cavitary lesion of pulmonary tuberculosis. Tuberculosis must be considered early in the differential diagnosis of these lesions and eliminated.[9] On the other hand, some of these patients with bronchogenic cysts have been considered to have tuberculosis and received treatment for this disease.[10-13] Since this lesion may be confused with tuberculosis, as well as occur in conjunction with tuberculosis, the experience with bronchogenic cyst at the Ohio Tuberculosis Hospital is reviewed.

*From the Ohio Tuberculosis Hospital and the Division of Thoracic Surgery, Department of Surgery, and Departments of Pathology and Radiology, The Ohio State University Health Center, Columbus, Ohio.
Presented at the 24th Annual Meeting, American College of Chest Physicians, San Francisco, June 18-22, 1958.

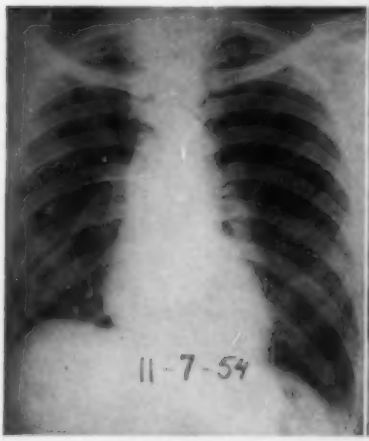

FIGURE 1

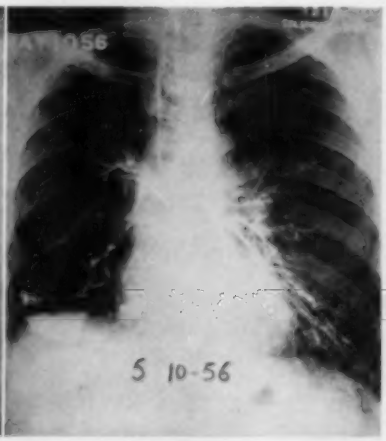

FIGURE 2

Figure 1 (Case 1): X-ray film obtained 15 months prior to admission. Note the multiple thin-walled cavities in the right lower lung field.—*Figure 2* (Case 1): Bilateral bronchogram shows several thin-walled cavities with wide bronchial communications in the right middle and lower lobes.

In a two-year period between November 1955 and November 1957, 225 pulmonary resections were performed at this hospital with the usual indication for surgery being residual tuberculous cavity. When the specimens were examined pathologically, the cavitary lesions in 14 patients were found to be bronchogenic cyst rather than tuberculous cavities. Twelve of the 14 patients were men and two were women. The ages ranged between 31 and 57 years. All had been sent to the hospital with a preadmission diagnosis of pulmonary tuberculosis, and all had received specific chemotherapy for tuberculosis for from 10 months to 16 years. Because of the probability of tuberculosis, all patients were continued on specific chemotherapy for this disease to the time of resection. The cyst was in the right upper lobe in eight patients, the left upper lobe in five, and the right lower lobe in one.

At the time of onset of disease these patients had symptoms compatible with pulmonary tuberculosis. Almost all had an acute onset with cough, sputum production and fever, and several had weight loss. Physical examination did not distinguish the disease process from tuberculosis. Sputum examinations were carried out repeatedly in all of these patients. In three acid-fast bacilli were never found in the sputum. Eight were found to

FIGURE 3 (Case 1): Gross photograph of resected specimen to show the large cysts in the lower lobe. At least two bronchial communications with each cyst can be seen.

have one isolated smear or culture positive for acid-fast bacilli, and three had sputum consistently positive for tubercle bacilli.

In addition to the specific chemotherapy for pulmonary tuberculosis which was received by all patients, one had received pneumothorax, seven had phrenic nerve interruption and one had been treated by thoracoplasty in an effort to close the supposed tuberculous cavity.

Radiologically almost all of the patients had extensive infiltration with the early demonstration of cavitary disease. The pulmonary infiltration was found to clear unusually rapidly after therapy for tuberculosis was instituted, leaving a thin-walled cavity or cavities which changed little in size, usually present in the upper lung fields. While on the standard roentgenogram these appeared as a solitary cavity in most of the patients, multiple cavitary lesions could be demonstrated in one. Laminagraphy, however, revealed multiple lesions in many of these patients as well as wide bronchial communications with the cysts. Bronchography was performed in a majority of these patients and appeared to be characteristic. The contrast medium flowed easily into the cyst, and in most instances several rather large bronchial communications could be demonstrated by the bronchographic technique. This is in direct contrast to the cavity of tuberculosis in which cavitary filling has been accomplished only rarely and multiple bronchial communications practically never demonstrated.

Case Reports

Details of three selected cases are presented to illustrate the clinical course of patients with bronchogenic cysts in whom tuberculosis was either absent or present.

Case 1: H. T., a 52 year old construction worker noted productive cough, fever and weight loss in 1934, which prompted his admission to a sanatorium for eight months.

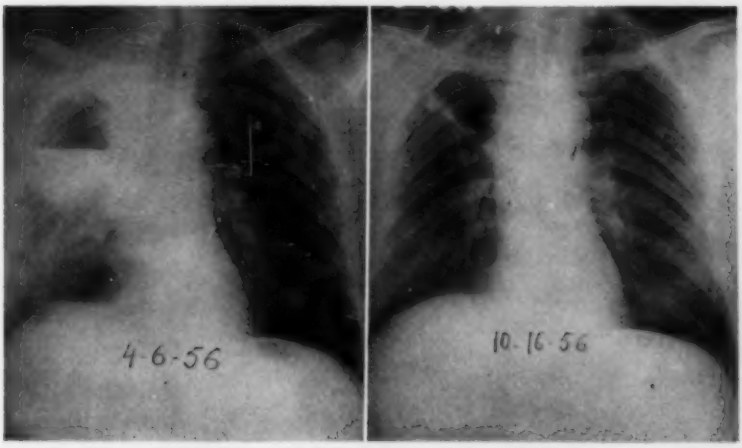

FIGURE 4 FIGURE 5

Figure 4 (Case 2): X-ray, obtained shortly after onset of symptoms, shows large, fluid-containing cavity in the right upper lobe, surrounded by dense infiltration. The rest of the right lung and the left lung show diffuse nodularity compatible with silicosis.—*Figure 5* (Case 2): Note the remarkable clearing in a relatively short period of time and the remaining large thin-walled cavity.

These symptoms recurred in 1944 and again in 1954 (Fig. 1), at which time he had hemoptysis, night sweats and chills. In October 1955 he was admitted to a sanatorium and was started on streptomycin and para-aminosalicylic acid (PAS). Acid-fast bacilli were not recovered from sputum by smear or culture. Radiogram of the chest showed multiple thin-walled cavitary lesions in the right lower lung field. He was admitted to the Ohio Tuberculosis Hospital for surgical consideration in April 1956, and three months later had right pneumonectomy. Preoperative bronchogram showed multiple cystic defects with wide bronchial communications (Fig. 2). Examination of the resected lung showed bronchogenic cysts without associated tuberculosis (Fig. 3). He was discharged without further chemotherapy.

Case 2: G. B., a 57 year old foundry worker had an acute febrile illness in March 1956 accompanied by sputum production and cough. No acid-fast bacilli were found in sputum by smear but one culture was positive for these organisms. He was started on isoniazid and PAS and admitted to a sanatorium. Roentgenogram then showed a large fluid-containing cavity in the upper lobe with infiltration in the remaining right lung (Fig. 4). Later films showed rapid clearing of the infiltration and persistence of the cavity in the right upper lobe (Fig. 5). Laminagraphy revealed a single cavity, while bronchogram demonstrated filling of this cavity with the contrast material. He was admitted to the Ohio Tuberculosis Hospital in October 1956, and in November right upper lobectomy was carried out because of the residual cavitary lesion. Pathologic examination of the resected lobe showed a bronchogenic cyst and nodular silicosis but no pulmonary tuberculosis. He was discharged from the hospital without further drug therapy.

Case 3: P. R., a 31 year old man developed productive cough, fever, night sweats and weight loss of 32 pounds in March 1954. He was started on streptomycin and PAS. Pneumoperitoneum was used as an adjunct to the chemotherapy. Subsequently isoniazid was added to this regimen and preoperatively cycloserine and pyrazinamide were substituted for these drugs. Two sputum smears showed the presence of acid-fast bacilli, but all cultures were negative. A radiogram of the chest taken at the time of onset of disease showed bilateral extensive infiltration with multiple cavities in both upper lung fields (Fig. 6). Clearing of the parenchymal infiltrate occurred rapidly after therapy, but bilateral apical cavitary lesions remained (Fig. 7). He was admitted for surgical treatment of the residual cavities in August 1957. Laminagraphy (Fig. 8) and bronchography on the right showed a cavitary lesion with large multiple bronchial communications. The cavity could be easily filled by contrast medium at the time of bronchogram (Fig. 9). The right upper lobe and the superior segment of the right lower lobe were resected on August 15, 1957. Examination of the resected specimen showed multiple bronchogenic cysts in association with chronic, inactive fibrocaseous pulmonary tuberculosis. Three months later the cavitary lesion in the left apex was resected. An open-healed tuberculous cavity was found. Because of the latter finding, chemotherapy for tuberculosis was continued.

FIGURE 6

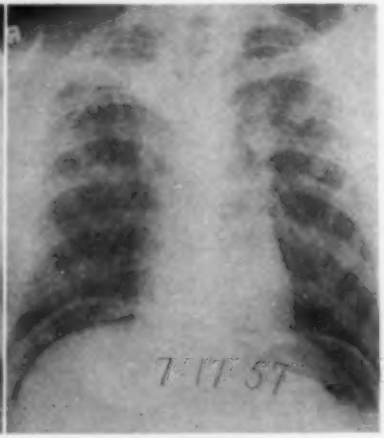

FIGURE 7

Figure 6 (Case 3): X-ray film at beginning of illness shows extensive bilateral dense infiltration with multiple cavities in both upper lung fields.—*Figure 7* (Case 3): There has been a marked improvement in the extensive bilateral infiltration (compare Figure 6) with persistent biapical cavities.

Although each of these patients was admitted to the hospital with a diagnosis of pulmonary tuberculosis, pathologic examination of the resected tissue revealed active tuberculosis in only three. Five of the remaining 11 cases were found to have minimal, inactive tuberculosis not in proximity to the bronchogenic cyst. One had nodular silicosis and five had no associated pulmonary lesions.

The diagnosis of bronchogenic cyst was made only if the cavitary lesion showed pseudostratified ciliated columnar epithelium on a distinct basement membrane (Fig. 10) together with either smooth muscle, mucous glands (Fig. 11), or cartilage in the wall of the cyst. At least one of the latter three elements was required to fulfill the diagnostic criteria of cysts in these 14 patients. This pathological entity is quite distinct from the so-called open-healed cavity of tuberculosis in which the lining and wall are composed of fibrous tissue. Further, this lesion is easily distinguished from the partially re-epithelialized tuberculous cavities in which squamous epithelium has grown along the fibrous wall of the lesion. In rare instances pseudostratified columnar epithelium may be present in these re-epithelialized cavities, but a basement membrane, smooth muscle, mucous glands and cartilage are not present except in the region of the communicating bronchus. If less rigid criteria were accepted for the diagnosis of bronchogenic cyst, several additional patients could have been included, but when the typical pseudostratified columnar epithelium and basement membrane were not present these cases were eliminated from this series. In 13 of the 14 patients the lining of the cyst was intact, while in one a single area of the wall was found to be the site of a tuberculous ulceration.

DISCUSSION

Many pathological processes of the lung parenchyma can be confused with pulmonary tuberculosis.[14] Cavitary lesions may be caused by tuberculosis, histoplasmosis, coccidioidomycosis, blastomycosis, abscess, cavitating primary or secondary tumors of the lung, blebs, bullae, or bronchogenic cysts, as well as other diseases. While some of

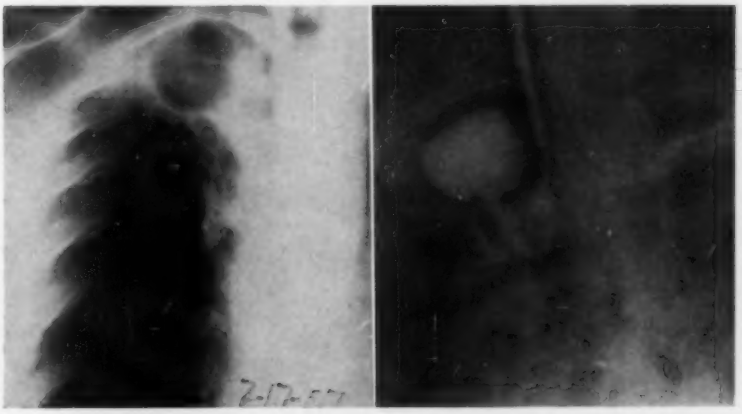

FIGURE 8 FIGURE 9

Figure 8 (Case 3): Laminagram showing large thin-walled cavity in the right apex. Note the minimal residual infiltration in the right lung.—*Figure 9* (Case 3): Bronchography—Spot view during fluoroscopy showing wide bronchial communication with the large right upper lobe cavity.

these have definite characteristic appearances, such as the thick, irregular wall in cavitating bronchogenic carcinoma and the line-thin wall of the bulla, all have at one time or another brought patients to the attention of a chest physician as a possible instance of pulmonary tuberculosis. The careful evaluation of the patient together with the finding of pyogenic bacteria, tubercle bacilli, of fungi or of malignant cells in the sputum helps establish the diagnosis, as does serial roentgenography.

The bronchogenic cyst represents a congenital or developmental abnormality of the lung. Although not occurring in the cases presented, evidence in support of this belief is the occasional occurrence of an abnormal systemic arterial blood supply to such lesions.[15, 16] In all probability bronchogenic cyst is present but unrecognized in many individuals. Most likely it exists as a slit-like defect in the parenchyma of the lung until infection occurs in the lumen and the adjacent tissue. With this infection it is postulated that sufficient change is exerted on the wall of the cyst to allow it to develop a lumen and become clinically detectable. While the ballooning of this lesion may result from temporary bronchial involvement producing a ball-valve action, the persistence of the space cannot be explained in this manner because of the wide bronchial communications that are easily demonstrated by bronchography. More likely there is sufficient fibrosis in the adjacent parenchyma of the lung to cause the expanded cyst to retain an annular form. Obviously the infection need not be tuberculosis, for pulmonary tuberculosis was found adjacent to the bronchogenic cyst in only three of the 14 patients. Yet the early roentgenogram in all of these patients showed extensive pulmonary infiltration.

While the current series represents a highly selected group of patients by virtue of the specialized nature of this hospital, an incidence of 6.2 per cent of bronchogenic cysts among patients presumed to have cavitary pulmonary tuberculosis makes the

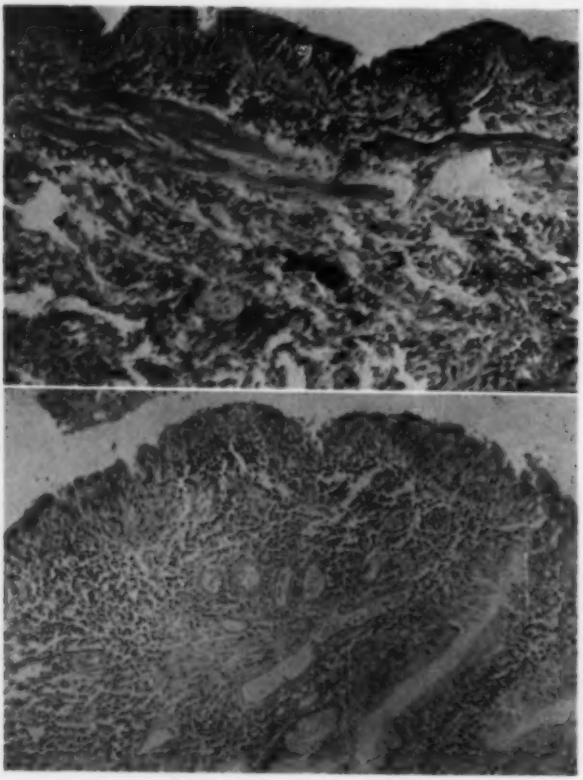

FIG. 10

FIG. 11

Figure 10: Photomicrograph showing characteristics of bronchogenic cyst wall. Note pseudostratified ciliated columnar epithelium, prominent basement membrane, and fibers of smooth muscle in wall (100 ×).—*Figure 11:* Photomicrograph showing characteristics of cyst wall. Note again the respiratory epithelium, and also the large mucous glands. There is diffuse lymphocytic infiltration in the wall (100 ×).

early identification of this lesion desirable. Clinical examination of the patients aids little in the differentiation of bronchogenic cyst from pulmonary tuberculosis. In a patient with untreated cavitary disease the absence of positive sputum for tubercle bacilli or the occurrence of an isolated positive smear or culture for acid-fast bacilli, which may or may not represent tubercle bacilli, is significant. The rapid clearing of the pulmonary infiltration following the institution of chemotherapy leaving a thin-walled cavitary lesion, especially when laminagraphy demonstrates multiple cysts and bronchography shows multiple bronchial communications with easy filling of the annular lesion with the contrast material, should suggest the possibility of bronchogenic cyst. This ease of filling of the bronchogenic cyst is in contrast to the findings of others[11] who found that bronchography was of no value since the cysts they described could not be filled with the contrast material. In the present series, however, the cyst was easily filled in all patients in whom bronchogram was carried out.

It is recommended that these lesions should be removed surgically, particularly in the younger age group, primarily because of the risk of recurrent infections. Other indications for removal of bronchogenic cysts are the possibility of hemorrhage or of perforation of the cyst into the pleural space, as well as the occasional development of carcinoma in the wall of the cyst.[17]

Collapse therapy is of no value and is not indicated. If the bronchogenic cyst is recognized, early surgical removal without the usual long-term specific chemotherapy for pulmonary tuberculosis should be accomplished. In those patients with associated pulmonary tuberculosis, the usual period of chemotherapy is indicated.

CONCLUSIONS

1. Bronchogenic cyst is a relatively common lesion in patients admitted to the surgical service of a tuberculosis hospital, with an incidence of 6.2 per cent in the series presented.
2. Most patients with this lesion did not have associated, active, pulmonary tuberculosis, even though receiving specific chemotherapy for tuberculosis for from 10 months to 16 years.
3. The diagnosis should be suspected in any patient with an annular lesion with minimal parenchymal involvement, particularly when the sputum studies have not confirmed the presence of pulmonary tuberculosis.
4. The diagnosis can be established in most instances by the use of laminagraphy and bronchograms which will show the presence of multiple cystic lesions with multiple bronchial communications.
5. Pathologically these lesions have ciliated columnar epithelium, a definite basement membrane and either mucous glands, smooth muscle, or cartilage within the walls.

CONCLUSIONES

1. El quiste bronquiogénico es relativamente común en los enfermos entrados a un servicio de tuberculosis por frecuencia de 6.2 por ciento en la serie que se presenta.
2. La mayoría de los enfermos con estos quistes no tenían tuberculosis activa aunque habían recibido quimioterapia para tuberculosis, desde 10 meses hasta 16 años.
3. Debe sospecharse el diagnóstico cuando hay aspecto anular con compromiso parenquimatoso mínimo, en particular cuando los exámenes de esputos no han confirmado la presencia de tuberculosis pulmonar.
4. El diagnóstico puede establecerse en la mayoría de los casos por la tomografía y broncografía que mostraron múltiples quistes con comunicación bronquial.
5. La histopatología muestra epitelio columnar ciliado con membrana basal y ya sean glándulas mucosas, músculo liso, o cartílago en las paredes.

RESUME

1. Le kyste bronchique est une lésion relativement commune chez les malades hospitalisés dans le service chirurgical d'un hôpital de tuberculeux. Le taux était de 6,2% dans la série que les auteurs rapportent.
2. La plupart des malades atteints de cette lésion n'avaient pas de tuberculose pulmonaire évolutive associée, même quand ils avaient été soumis à un traitement chimiothérapique spécifique antituberculeux qui selon les cas avait été continué de 10 mois à 16 ans.
3. Le diagnostic devrait être mis en doute chez tout malade atteint d'une lésion annulaire avec atteinte parenchymateuse minime, particulièrement quand les études d'expectoration n'ont pas confirmé la présence de tuberculose pulmonaire.
4. Le diagnostic peut être établi dans la plupart des cas par l'utilisation de la laminagraphie et de bronchographies qui montreront la présence de lésions kystiques multiples avec communications bronchiques multiples.
5. Du point de vue anatomo-pathologique, ces lésions ont un épithélium cilié, une couche sous-épithéliale nette, avec soit des glandes muqueuses, soit des muscles lisses, soit du cartilage à l'intérieur de la paroi.

ZUSAMMENFASSUNGEN

1. Die bronchogine Cyste ist ein relativ häufiger Befund bei Kranken, die in die chirurgische Abteilung eines Tuberkulose-Krankenhauses überwiesen werden, mit einer Häufigkeit mit 6,2% in den vorgelegten Fällen.

2. Die meisten Kranken mit diesem Befund hatten keine damit verknüpfte aktive Lungentuberkulose, obwohl sie eine spezifische Chemotherapie wegen Tuberkulose erhielten während einer Zeitspanne von 10 Monaten bis 16 Jahren.

3. Man muss diese Diagnose vermuten bei jedem Kranken mit einer ringförmigen Läsion mit minimaler Beteiligung des Parenchyms, besonders dann, wenn die Sputumuntersuchungen das Vorliegen einer Lungentuberkulose nicht bestütigen.

4. Die Diagnose lässt sich in den meisten Fällen ermöglichen durch Anwendung von Schichtaufnahmen und Bronchogrammen; diese zeigen das Vorhandensein von multiplen cystischen Herden mit multiplen Bronchusverbindungen.

5. Pathologisch-histologisch bestehen diese Veränderungen aus einem cystischen Klimmerepithel, einer deutlichen Basalmembran und entweder Schleimdrüsen, glatter Muskulatur oder knorbelhaltigen Wänden.

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The Influence of Instrumental Resistance on the Maximum Breathing Capacity*

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Since Hermannsen[1] first described the test for maximal ventilation capacity in 1933, its estimation has become one of the most widely applied tests of respiratory function. However, the results of the test may be considerably influenced by the resistance of the test apparatus, its fidelity at high frequencies, and by the motivation of the subject. Although the importance of an instrument of suitable frequency response and resistance has been recognized, there have been few attempts to measure these characteristics in the various instruments used, nor is it clear to what extent a particular instrumental resistance will influence the results obtained.

This paper describes an investigation of the resistance characteristics of three types of apparatus employed for this test and a study designed to estimate the extent by which instrumental resistance may influence the test results.

Apparatus Tested:

The following methods of estimating the maximum breathing capacity were examined:

a) *Douglas bag method*,[2] using a standard Douglas bag with a neck of 24 cm. in length and 2.8 cm. internal diameter, a standard Siebe-Gorman three-way valve of 1.8 cm. bore set for straight-through flow during a test and a box-valve of proved low resistance which has been described elsewhere.[3]

b) *Spirometric method:* Many different spirometers have, in the past, been used for this test. The most suitable commercial model* available to us had wide bore tubing (3.25 cm.), a bell of low mass (250 gm.) and wide diameter (20.5 cm.) and a small gap between the bell and inner core (0.8 cm.).

c) *Gasometer method:* This apparatus (Figure 1) consisted of a modified domestic gas meter** attached by 120 cm. of wide bore tubing (3.0 cm. internal diameter) to the inflow vent of the box-valve already referred to. It was, thus, a modification of the apparatus described by McKerrow,[4] but differed in that measurement was made of inspired air. Apart from the box-valve, which was easily washed and sterilized, it remained uncontaminated by expired gas. As in McKerrow's instrument, a bellows was attached between the box-valve and meter with the object of converting intermittent to semi-continuous flow. The apparatus was tested both with and without the bellows attached.

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*Lode Spirometer, Instrumenten Lode N. V., Groningen, Nederland.
**Parkinson and Cowan, Dry Test Meter, Catalogue No. R. Type "C," Model D4.

All maximum breathing capacity (MBC) tests were performed with a nose clip and wide bore mouthpiece of 5 cm^2 cross sectional area. A 10 second test period was employed with the subject in a sitting posture and results were reported in liters per minute at body temperature, atmospheric pressure and saturated with water vapour (BTPS). Subjects were required to breathe as deeply as possible and then to increase their rate to a maximum, but no attempt was made to fix the respiratory rate.

Instrumental Resistance:

Studies were made of the resistance of each type of apparatus by inserting a Lilly pneumotachograph between the mouth and the apparatus under test while subjects breathed at varying frequency and depth. Comparison was made of instantaneous flow and pressure* across the apparatus. In the case of the Douglas bag and Lode spirometer, condensation of moisture on the pneumotachograph screen was avoided by inserting a bag-box system between the instrument and the mouth. In the case of the gasometer, only inspiratory resistance was measured as expiration passed through the valve box only, the resistance of which was already known.[3]

The pressure flow characteristics of each instrument are represented in Figure 2. For purposes of comparison, both negative and positive pressure (corresponding to inspiration and expiration respectively) are recorded with the same sign.

At equivalent flow rates the pressure developed in the Douglas bag system was highest, with successively lower values for the gasometer with bellows attached, and the Lode spirometer. By contrast, the resistance of a Benedict-Roth spirometer studied by Shephard[5] is very high and has been plotted for comparison.

These results indicate no more than the resistances of the particular instruments assembled for this study. Thus, the use of the Douglas bag technique should not necessarily be condemned because of the high values obtained. It does demonstrate, however, that if this test is performed

*Statham, P. 5 TC 0.7 psid.

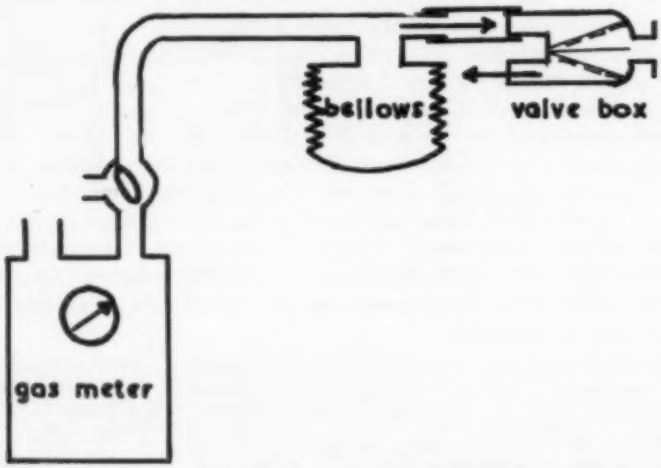

FIGURE 1: Diagram of apparatus for the gasometer method of measurement of MBC.

with the standard equipment used in this study, instrumental resistance is liable to be high. To what extent such resistance may influence results is assessed below.

The Influence of Instrumental Resistance on MBC Values:

An experiment was next performed to define, as far as possible, the extent to which instrumental resistance might be expected to influence test results. Measurements of MBC were carried out four times on each of 16 untrained normal healthy subjects and on 16 patients who all had low maximum breathing capacity values due to such factors as emphysema, bronchospasm and obesity. The gasometer apparatus with bellows was used throughout with a deadspace between the mouthpiece and the valve to conserve CO_2. This instrument, either alone or with one of three added resistances at the mouthpiece, provided four grades of resistance for each subject. After a preliminary trial the tests were carried out with a five minute rest between each, the order of tests being carefully randomized to eliminate the influence of learning and fatigue on the group mean results.

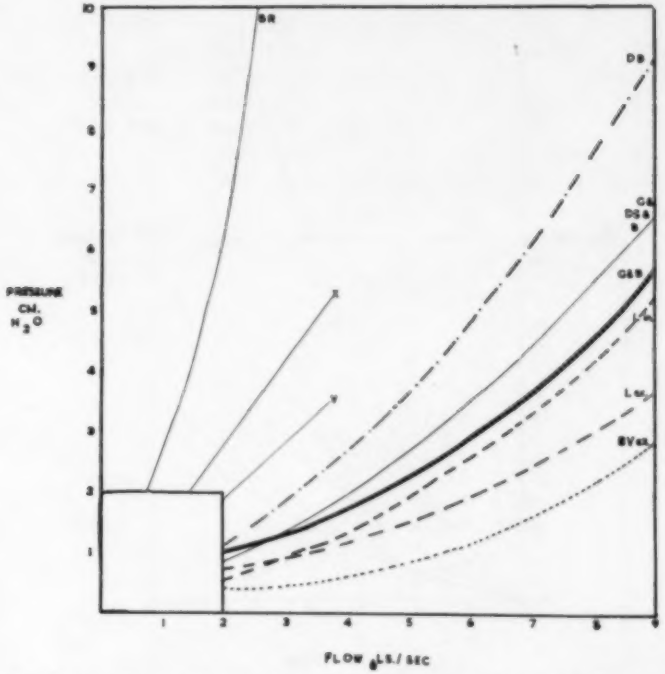

FIGURE 2: Flow resistance in various apparatuses used for the measurement of MBC.

BR	— Benedict-Roth spirometer tested by Shephard.
DB	— Douglas bag method.
G and DS and B	— Gasometer method with bellows and added deadspace.
G and B	— Gasometer method with bellows.
L in	— Lode spirometer (inspiratory resistance).
L ex	— Lode spirometer (expiratory resistance).
BV ex	— Box-valve (expiratory resistance).
X and Y	— Resistance lines established by McKerrow. Resistances less than line Y were found by him to produce an insignificant effect on MBC values, those above line X to reduce MBC significantly.

The pressure flow characteristics of the gasometer with bellows and deadspace (Control) and with each of the added resistances (R_1, R_2, R_3) is plotted in Figure 3. The effect of these added resistances on MBC values is seen in Figure 4 in which the mean MBC values at each added resistance have been recorded as a percentage of the control value obtained without added resistance.

It is noteworthy that a resistance (R_3) considerably lower than that of the Benedict-Roth spirometer has resulted in a reduction of nearly 30 per cent in the mean MBC value of the patient group. However, it is apparent from comparison of Figures 2, 3 and 4 that the resistances encountered in the gasometer apparatus and Lode spirometer are unlikely to cause significant reductions in MBC values. The Douglas bag apparatus has a resistance somewhat greater than the artificial resistance R_1 and less than R_2 and might be expected to cause reductions in test scores. This point is considered further below.

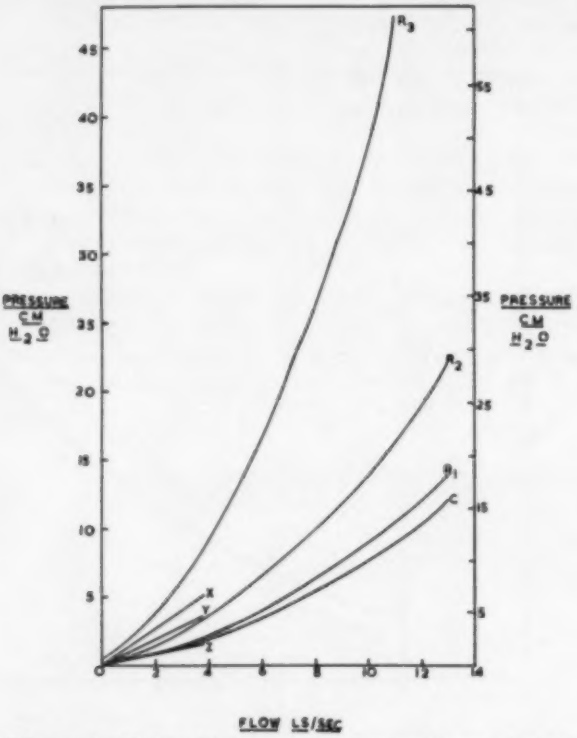

FIGURE 3: Effects of added resistances on the flow resistance characteristics of the gasometer and bellows.

Flow resistance characteristics of the gasometer with bellows and an added deadspace are represented by line C. The lines R_1, R_2 and R_3 are the flow resistance characteristics in this circuit with added resistances.

Left hand Y-axis — pressures recorded by present workers at an altitude of 5,760 feet above sea-level.

Right hand Y-axis — estimated pressures which might develop in the same apparatus at sea-level. The calculations assume totally turbulent flow at all velocities.

X, Y and Z — resistance lines established by McKerrow. X and Y as in Figure 2. Z represents resistance of his "ideal" apparatus.

TABLE I—MBC RESULTS IN NORMAL MALES
(Derived from reports in the literature)

		Age (Years)			
		Mean	Range	No. of Cases	MBC L/Min. BTPS (Mean Values)
Baldwin et al. (1948)	Modified Benedict-Roth spirometer	25.5	16-34	17	126
Gray et al. (1950)	Modified Benedict-Roth spirometer	23.1	—	283	167
D'Silva and Mendel (1950)	Modified Knipping spirometer	23.7	19-32	15	188
Bernstein et al. (1952)	Aluminium bell spirometer	24	20-33	14	193
Needham et al. (1954)	Standard Douglas double valve-box and 100 L Douglas bag	25.2	20-30	27	148
Anderson et al. (1953)	High velocity valve Douglas bag	—	16-34	38	172
Gilson and Hugh-Jones (1955)	"Simple vital capacity spirometer"	24.8	24-28	10	150
Shephard (1957) (18)	Modified Pneumotachograph	24.5	20-30	15	175

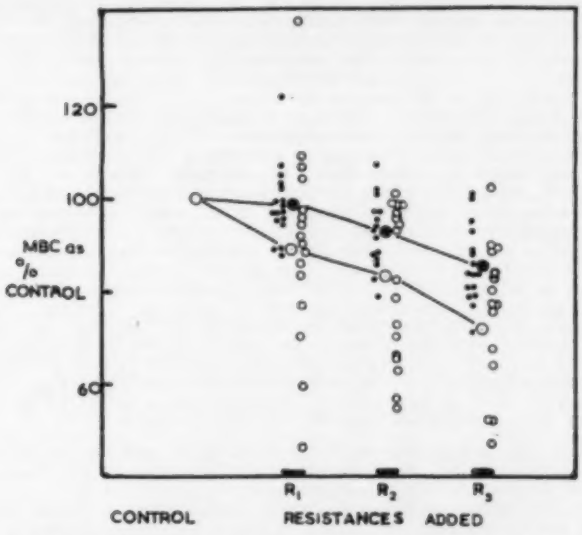

FIGURE 4: The effect of added resistance on MBC values in 16 healthy normal subjects (closed circles) and in 16 patients (open circles).

All values were expressed as a percentage of the MBC measured on the apparatus without added resistance, hence control values are all 100%. Two lines drawn through the mean values for each resistance indicate the extent of the decrease of MBC in the normal and abnormal subjects respectively.

Although there is considerable overlap between the healthy and patient groups, it would appear that added resistance has affected the patient group to a greater extent. This is the result of representing changes as a percentage of control values, the patient group having had lower control MBC values.

DISCUSSION

Review of the literature reveals wide variations in the reported normal figures for MBC (Table I). This is undoubtedly in part due to differences in procedure. Thus, some workers performed the test with the patient standing[6, 7] and others sitting,[8, 9] some fixing the breathing frequency at an arbitrary rate,[10] or predicting the optimum rate from the timed vital capacity.[11] However, differences in instrumentation are probably even more responsible for this variation between different laboratories. The importance of an adequate frequency response for spirometer systems has been widely accepted following the studies of Mendel and his colleagues.[5, 10] The spirometer used in this study was tested by us and found to be accurate to within 2 per cent up to a frequency of 118 cycles/minute, while the gasometer apparatus remained accurate within these limits up to the highest frequencies tested (170 cycles/minute).

The influence of instrumental resistance on test results has also received some study. Matheson and associates[12, 13] demonstrated that the average ventilation capacity of eight healthy subjects could be lowered from 186 L/minute to 33 L/minute by adding extra resistances to their equipment but the values of these resistances were not recorded. McKerrow (quoted by Cotes[14]) using seven healthy trained subjects showed that resistances lower than the line "Y" (Fig. 3) produced an insignificant effect on the MBC. The present study suggests, however, that when untrained normal controls or patients are tested, a resistance of this order (which corresponds closely to R_2 in figure 3) may cause a significant reduction in MBC values.

Bartlett and Specht[15] studied the influence of six added resistances on the MBC values of three normal laboratory workers. When these resistances were added, as in our study, between the mouthpiece and the box-valve, roughly comparable reductions in MBC resulted. They demonstrated, however, that the influence of added resistance on the expiratory side alone, as is the case in the Douglas bag method, had far less influence on MBC values. One can conclude that in selecting equipment for the measurement of MBC a resistance against inspiration should be kept below the line R_1 (Fig. 3) though it is clear from the work of Bartlett and Specht that higher resistances may be allowed if on the expiratory side of the apparatus only.

Finally, in a study such as this done at 5,760 feet altitude the influence of air density on resistance values must be considered. MBC values recorded at altitude are higher than those recorded with similar techniques at sea-level.[16, 17] The lower gas density at this altitude may be expected to cause reductions in both the internal work of breathing and in the pressure flow characteristics of the instruments used. From the work of Cotes[14] it is possible to estimate that at 6,000 feet the work of breathing may be so diminished as to produce an increase in MBC values of the order of 6 per cent over sea-level values. The instruments tested in this study have not been observed in a pressure chamber to simulate sea-level conditions, but some idea of the maximum order of change which might be anticipated may be obtained by application of formulae applicable to resistance in smooth pipes. To give some idea of the likely pressure flow relationships of the instruments tested in this study, the maximum possible pressures which could be developed at sea-level (assuming fully turbulent flow), are graphed on the right hand Y-axis of Figure 3. These can be contrasted with the figures on the left hand Y-axis which are the pressures measured at equivalent flows in the apparatus at 5,760 feet. These figures involve too many assumptions to be considered at all exact, but they do suggest that considerable changes may be expected in instrumental characteristics even at moderate altitudes. That these assumptions are not grossly inaccurate is suggested by the fact that the resistance developed in a standard Douglas bag at sea-level is shown in the graphs of Bartlett and Specht[15] to be approximately 6 cm. of water at a flow rate of 5 liters per second, while the pressure developed at the same flow in our standard Douglas bag was only 3.6 cm. of water. This is the order of difference which might be anticipated from comparison of the right and left hand "Y" axes of Figure 3.

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SUMMARY AND CONCLUSION

The pressure flow characteristics of three types of apparatus used in the measurement of MBC have been tested. They are all low when compared to the standard Benedict-Roth spirometer, though that of a standard Douglas bag and valves was considerably higher than that of the spirometer or gasometer tested.

The influence of increments of airway resistance on MBC values was assessed in 16 normal subjects and 16 respiratory patients. Resistances corresponding to the line "R_1" in figure 3 when added to inspiration and expiration caused a negligible reduction in these values. Greater increments could not be added without significantly reducing the MBC values, especially in some of the patients. Judging by these criteria, both the spirometric and gasometer techniques appeared to have adequately low resistances. Although the resistance of the Douglas bag method was higher, this resistance was only on the expiratory side of the circuit where, according to the work of Bartlett and Specht, it would also have an insignificant effect on MBC values. However, the resistance of the Benedict-Roth spirometer was sufficient to cause considerable reduction in these values.

RESUMEN Y CONCLUSIONES

Se probaron las presiones del flujo características en tres tipos de aparatos para la medida de Capacidad Respiratoria Máxima. Todos fueron bajos cuando se compararon al espirómetro estandar de Benedict-Roth aunque el de uno de Douglas estandard de bolsa y de válvulas, la tenía mayor que las de los espirómetros o gasómetros probados.

La influencia de los incrementos de la resistencia de las vías aéreas los valores de la Capacidad Respiratoria Máxima (CRM) se estimó en 16 sujetos normales y en 16 enfermos respiratorios. Las resistencias correspondientes a la línea "R1" en la figura 3 cuando agregados a la inspiración y a la expiración causaron una reducción desdeñable de esos valores. Mayores incrementos no pueden agregarse sin reducir considerablemente los de la CRM especialmente en algunos de los enfermos.

De acuerdo con este criterio tanto la técnica de el espirómetro como la del gasómetro, parecen tener resistencias bajas y adecuadas.

Aunque la resistencia del aparato de bolsa de Douglas fué más alta, esta resistencia fué sólo en el lado expiratorio del circuito donde de acuerdo con el trabajo de Bartlett y Specht, habría un efecto insignificante sobre los valores de la CMR. Sin embargo, la resistencia del espirómetro de Benedict-Roth fué suficiente para causar una considerable reducción de esos valores.

RESUME

Les caractéristiques de pression de trois types d'appareils utilisés pour la mesure de la ventilation maximale ont été testées. Ils sont tous faibles lorsqu'on les compare au spiromètre standard de Benedict-Roth, bien que les pressions données par l'appareil standard avec réservoir et valves de Douglas soient considérablement plus élévées que celles du spiromètre ou gasomètre testé.

L'influence de l'augmentation de la résistance de l'air sur les valeurs de la ventilation maximale a été évaluée chez 16 individus normaux et chez 16 personnes atteintes d'affections pulmonaires. Les résistances correspondant à la ligne "R I" dans le schéma 3 lorsqu'elle s'ajoute à l'inspiration ou à l'expiration provoque une réduction négligeable de ces valeurs. Des augmentations plus grandes ne pourraient pas être ajoutées sans réduire d'une façon nette les valeurs de la ventilation maximale particulièrement chez certains malades.

En jugeant d'après ces critères, les techniques à la fois spirométriques et gasométriques semblent avoir des résistances également basses. Bien que la résistance obtenue par la méthode du réservoir de Douglas soit plus élevée, cette résistance n'agit que sur la partie expiratoire du circuit où, selon le travail de Bartlett et Specht, elle aurait également un effet insignifiant sur les valeurs de la ventilation maximale. Cependant, la résistance du spiromètre de Benedict-Roth a été suffisante pour provoquer une réduction considérable de ces valeurs.

ZUSAMMENFASSUNGEN

Es wurden die Druckstrom-Kurven von 3 Arten von Gefässen geprüft, die zur Messung des Atemgrenzwertes (AGW) dienen. Sie sind alle niedrig im Vergleich zum Standard-Benedikt-Roth-Spirometer, obwohl diejenigen mit einem Standard-Douglas-Beutel und mit Klappen beträchtlich höher waren als die des geprüften Spirometers oder Gasometers.

Es wurde der Einfluss einer Steigerung des Widerstandes in den Luftwegen auf den AGW ausgewertet bei 16 normalen Personen und bei 16 Patienten mit Erkrankung des Respirationstraktes. Der Linie "R_1" in Figur 3 entsprechende Widerstände ergaben, wenn sie der Inspiration und Expiration hinzugefügt wurden, eine unbedeutende Reduzierung dieser Werte. Grössere Widerstände konnten nicht hinzugenommen werden ohne beträchtliche Reduzierung des AGW, besonders bei einigen dieser Patienten. Von diesen Kriterien ausgehend scheinen sowohl die spirometrischen wie die gasometrischen Techniken entsprechend niedrige Widerstände zu haben. Obwohl der Widerstand des Douglas-Beutel-Verfahrens höher lag, befand sich dieser Widerstand nur auf der expiratorischen Seite des Kreises, auf der entsprechend den Arbeiten von Bartlett und Specht-ernur einen unbedeutenden Einfluss auf den AGW hat. Der Widerstand des Benedikt-Roth-Spirometers reicht jedoch aus, um eine beträchtliche Herabsetzung dieser Werte zu bewirken.

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Chemotherapy for the Tuberculin Converter: Results of a Survey of Attitudes Among 424 Tuberculosis Hospitals in the United States*

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Persons whose reaction to tuberculin has changed from negative to positive are known as tuberculin converters. There is widespread interest in chemotherapy for tuberculin converters as a means of preventing the development of clinical tuberculosis. Drug therapy of this kind is referred to as chemoprophylaxis. The effectiveness of chemoprophylaxis is thought to be greatest when offered to those whose tuberculin reactions are known to have changed from negative to positive within the previous year.

Robinson, Meyer and Middlebrook[1] were the first to report a pronounced decrease in the skin hypersensitivity of four infants to tuberculin during treatment with isoniazid. In each instance the reaction became negative to old tuberculin in a dilution of 1:100. Though few in number, their series of cases was of considerable interest to all who are intrigued with the idea of treating tuberculous infection in its earliest recognizable stage. So far, results have not been reported of the studies that are being made on a large scale by the United States Public Health Service.

Conduct of the Survey

Our curiosity about the prevailing attitude of our colleagues toward the treatment of tuberculin converters caused us to include a specific inquiry in a questionnaire mailed in 1956 to tuberculosis hospitals throughout the United States. The question was: *What is your policy regarding chemotherapy for persons (employees, contacts, etc.) whose tuberculin reactions change from negative to positive within a year but who show no evidence of active tuberculosis by x-ray or other examination?* For the convenience of the respondents, multiple-choice answers were provided.

The remainder of the questionnaire was concerned with policies and practices governing chemotherapy for patients following their dismissal from tuberculosis hospitals. Results of the survey are recorded elsewhere.[2]

The questionnaire was mailed to 519 institutions that met our criteria for inclusion in the survey. We required that they provide definitive care for tuberculosis. They must not be short-term diagnostic or surgical units, tuberculosis divisions of mental hospitals, or units operated by the armed forces. We received replies from 424 hospitals (figure). This represents an 81.7 per cent response.

Responses to the question are organized in the table in terms of the multiple-choice answers provided in the questionnaire.

*This survey was made possible in part by a grant from the Tuberculosis and Health Associations of the counties of Dakota, Freeborn, Goodhue, Mower, Olmsted, Rice, Steele and Washington in the State of Minnesota. These counties comprise the district served by Mineral Springs Sanatorium.

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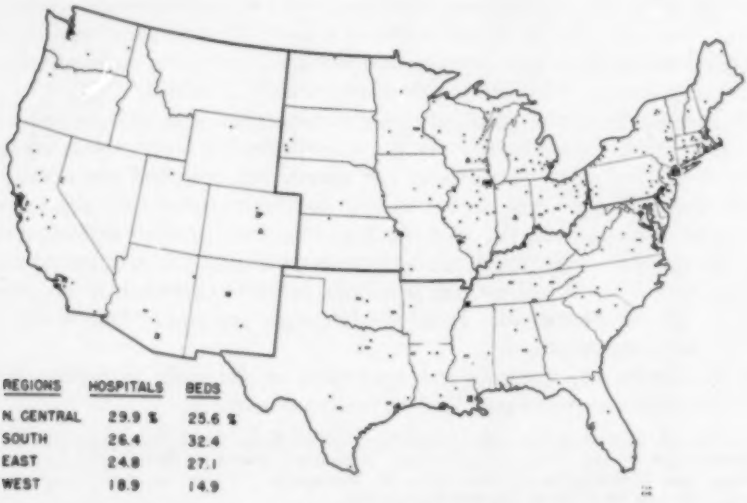
Attitudes Toward Treatment of the Tuberculin Converter

The respondents for 51.2 per cent of the hospitals said they do not offer chemoprophylaxis to the tuberculin converter unless a tuberculous lesion develops. On the other hand, those responding for 11.1 per cent of the hospitals stated that they prescribe treatment for all converters. An additional 23.3 per cent of the hospitals recommend chemoprophylaxis for selected cases. The respondents for 10 of the latter hospitals described the type of case selected for chemoprophylaxis: six limit treatment to infants, children or adolescents; two limit treatment to nurses or contacts of known open cases; one limits treatment to diabetic persons or to persons requiring steroid therapy; and one limits treatment to anyone converting within 6 months. From comments appended to a number of responses, it would appear that isoniazid is the drug of choice. In no instance did we sense that hospitalization was recommended as a part of the treatment of the tuberculin converter who presented no evidence of clinical tuberculosis.

The attitude toward treatment of tuberculin converters appears to be more conservative in hospitals located in the East and South than in hospitals located in the West and North Central regions of the country. Several respondents for one group of hospitals said that the policy governing operation of their hospitals did not permit treatment of tuberculin converters unless a tuberculous lesion appeared; therefore, they had to state this in their answers to the questionnaire; but they said that they, personally, favored the treatment of tuberculin converters without waiting for evidence of clinical tuberculosis.

We received qualified answers from 21 hospitals (5.0 per cent of the total). Most of these indicated two choices in the management of tuberculin converters. The respondents for 15 hospitals said that no treatment was offered unless the converters generated tuberculous lesions. Twelve



Location of 424 hospitals with 84,346 beds for tuberculosis. Each dot represents the location of one tuberculosis hospital. Heavy lines divide the map into the four regions defined by the Bureau of the Census.

TABLE I
POLICY REGARDING CHEMOTHERAPY FOR TUBERCULIN CONVERTERS

Policy regarding chemotherapy for tuberculin converters	Total hospitals		Bed capacity				Regional location*			
	Number	Per cent	Less than 100	100 to 299	300 to 499	500 or more	North Central	South	East	West
No treatment unless a tuberculous lesion appears	217	51.2	53.7	49.5	62.4	33.3	42.5	55.4	66.7	38.7
Offer treatment to selected cases only	99	23.3	20.6	27.2	14.6	27.8	29.9	20.5	15.2	27.5
Offer treatment to all cases	47	11.1	8.8	11.1	10.4	22.2	14.2	7.1	6.7	17.5
Undecided	31	7.3	7.5	7.2	6.3	8.3	7.1	8.9	3 8	10.0
Other	1	0.2	0.0	0.0	0.0	2.8	0.0	0.9	0.0	0.0
Qualified answer	21	5.0	6.9	2.8	6.3	5.6	6.3	2.7	5.7	5.0
No answer given	8	1.9	2.5	2.2	0.0	0.0	0.0	4.5	1.9	1.3
Total hospitals per cent		100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
number	424		160	180	48	36	127	112	105	80

*Regions as defined by the Bureau of the Census.[3]

of these, however, also indicated that they would prescribe treatment in selected cases: in most instances they recommended the treatment of children, and in one instance treatment was advised for contacts who are tuberculin converters.

Comment

The results of the survey reported in this article indicate current policies guiding the chemoprophylaxis of tuberculosis among specialized institutions—the tuberculosis hospitals. If encouraging results are observed from the treatment of large numbers of tuberculin converters in properly controlled studies, the attitude toward the chemoprophylaxis of tuberculosis in the United States probably will become less conservative. Those who prefer to withhold therapy until a tuberculous lesion appears may change their opinion and offer treatment to properly selected persons with tuberculosis in its preclinical stage.

SUMMARY

Answers were returned from 424 tuberculosis hospitals in the United States in a survey of policies in 1956 concerning treatment for the tuberculin converter—the person whose tuberculin reaction changes from negative to positive within a year, but who presents no evidence of active tuberculosis by x-ray film or other examination.

Respondents for 51.2 per cent of the hospitals do not offer treatment unless a tuberculous lesion develops, 11.1 per cent prescribe treatment for all cases of tuberculin conversion while 23.3 per cent restrict treatment to selected cases (infants, children or adolescents; nurses, contacts, persons with diabetes mellitus or persons who require steroid therapy, etc.). Isoniazid appears to be the drug of choice in the treatment of tuberculin converters.

RESUMEN

En contestación a una encuesta que se hizo en 1956 entre hospitales de tuberculosis en los Estados Unidos respecto de su actitud ante el uso de la tuberculina—las personas cuya reacción negativa vira a positiva, en el término de un año, pero que no presentan evidencias de tuberculosis activa se obtuvieron las respuestas de 424 hospitales.

51.2 por ciento de los hospitales que contestaron, no aconsejan tratamiento a menos que se presente una lesión tuberculosa; 11.1 por ciento prescriben tratamiento para todos los casos cuya tuberculino reacción negativa vira y 23.3 por ciento limitan el tratamiento a casos selectos (infantes, niños o adolescentes, enfermeras, contactos, personas con diabetes, o personas que necesitan tratamiento con esteroides, etc.). La isoniacida parece ser la droga de elección para los reactores recientes.

RESUME

Les auteurs ont pu recueillir les réponses de 424 hôpitaux tuberculeux des Etats-Unis sur la façon dont été traités en 1956 les virages de réactions tuberculiniques (personnes dont les réactions tuberculiniques étaient devenues positives pendant l'année, mais qui n'ont montré aucune manifestation de tuberculose active par les films radiologiques ou lors d'autres examens).

51,2% des hôpitaux qui avaient répondu ne donnaient pas de traitement à moins qu'une lésion tuberculeuse ne se développe, 11,1% prescrivaient un traitement pour tous les cas de virage, tandis que 23,3% restraignaient le traitement à des cas choisis (bébés, enfants ou adolescents; infirmières, personnes en contact avec des tuberculeux, personnes atteintes de diabète sucré ou personnes qui avaient besoin d'une hormonothérapie, etc.). L'isoniazide semble être la médication de choix dans le traitement des virages de réactions tuberculiniques.

ZUSAMMENFASSUNG

Es wurden von 424 Tuberkulose-Anstalten der USA Antworten erteilt auf eine Übersicht der Verfahren von 1956 hinsichtlich der Behandlung von Tuberkulinkonvertoren—d.h. solchen Personen, deren Tuberkulinreaktion innerhalb eines Jahres wechselte von negativen zu positiven Ausfall, die aber keine Anhaltspunkte für eine aktive Tuberkulose durch Röntgenaufnahme oder andere Untersuchungen boten.

51,2% der antwortenden Anstalten empfehlen keine Behandlung, sofern sich keine tuberkulösen Herde entwickeln, 11,1% schreiben eine Behandlung vor für alle Fälle von Umkehr der Tuberkulinreaktion, während 23,3% die Behandlung beschränken auf ausgewählte Fälle (jüngere und ältere Kinder oder Jugendliche, Pflegepersonal, Umgebungsfälle, Personen mit Diabetis oder solche, die eine Steroidbehandlung benötigen). INH scheint das Mittel der Wahl zu sein für die Behandlung der Tuberkulinkonvertoren.

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Varieties of Acid Fast Bacilli and Their Relationship to Disease in Man

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Less than a century ago it was found that leprosy and tuberculosis were due to bacteria which, when stained, could not be decolorized, even with acids. Since that time many other kinds of acid fast bacilli have been discovered. Some of these are parasites which evoke disease only in man or in man and other mammals. Some cause lesions in various warm or cold blooded animal species while others are entirely saprophytic, living freely on animal secretions or excretions, on plants, or even in soil, water and other inanimate materials. Recognition of the differences between the various mycobacterial species have been greatly facilitated by recently introduced methods for their investigations.

The acid fast bacillus of human leprosy, *M. leprae*, was described a decade before the discovery of the tubercle bacillus. Differences in the form and staining properties of these two kinds of acid fast bacilli were pointed out by Koch in his original presentation in 1882.

The bacillus of rat leprosy, or Stefansky's bacillus, is a similar acid fast organism which is found in smears or sections from nodules or other lesions in rats or mice. Neither the human nor the rodent leprosy bacilli have yet been successfully cultivated, and the various acid fast and other bacteria which have been obtained from leprous lesions are probably contaminants, and not the cause of the disease.

The bacillus of bovine enteritis, or Johne's bacillus, is an acid fast organism which may be cultivated from intestinal discharges or other specimens from affected cattle or sheep only after long incubation on complex media to which has been added an extract of killed mycobacteria.

Mycobacterium ulcerans is another acid fast bacillus which does not grow under the usual bacteriological techniques. It may be cultivated on glycerol-free medium at temperatures below 33°C, but not in the ordinary incubator temperature of 37°C. It was first found in ulcerative skin lesions in men and animals in Australia, and later in other countries.

M. balnei is an acid fast bacillus which also grows best at temperatures lower than that of the human body, though it may be adapted to grow at 37°C. It has been found in keratotic skin lesions in persons using certain swimming pools, and from the water or sides of the pools in some instances.

Acid fast bacilli which have been seen in skin lesions, lymph nodes and other materials from tuberculin reacting cattle and guinea pigs but which have not been successfully cultivated might have grown, in some instances, if special cultural techniques had been used.

All acid fast bacilli are also alcohol fast, and therefore apparently gram positive, non-sporulating, non-encapsulated, non-motile, and non-branch-

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ing. All tubercle bacilli are mesophilic, aerobic, slow growing, produce discrete, opaque, white or cream colonies, which contain much lipid, reducing enzymes, and tuberculin, and cause sensitization, immunity, and usually lesions in susceptible species.

Human tubercle bacilli differ from all other acid fast bacteria by their high niacin content. Typical virulent human tubercle bacilli are eugonic, glycerophilic, rough, neutral red positive, tightly corded, peroxidase and catalase positive, with moderate urease, arylsulfatase and indophenol dehydrogenase activity. They are inhibited by streptomycin, isoniazid, para-amino-salicylic acid, amithiazone, viomycin, neomycin, pyrazinamid, and cycloserine, and are susceptible to lyses by bacteriophages D28, D29, D32, D34, D55 and D56. They are highly pathogenic for guinea pigs and also for mice on intravenous inoculation, but have low virulence for rabbits and cattle, and none for fowl.

Human tubercle bacilli may undergo considerable variation either *in vitro* or *in vivo*, spontaneously or through selective factors such as chemotherapy. Thus they may become dysgonic, growing more slowly, or they may grow at an increased rate, they may yield smoother colonies, give only a pinkish instead of a deep red with neutral red and only a loose cording on microculture, may become resistant to any of the drugs to which they have been exposed, lose their peroxidase or catalase enzymes, and be attenuated, or entirely lose their virulence for guinea pigs, but still be recognizable as human tubercle bacilli.

The bacillus of bovine tuberculosis resembles the human strains in many respects, but is usually more dysgonic and glycerophobic, fails to grow in Besredka's liquid egg yolk medium, produces characteristic umbilicated or "doughnut" shaped colonies on Bordet-Gengou medium, which are non-pigmented, shows a characteristic Theobald Smith acidity curve in glycerol broth and is more resistant to PAS and Amithiazone, but these characteristics may not be consistent, especially after repeated transfers. The absence of niacin and the greater virulence for rabbits are more reliable distinctions.

Bovine tubercle bacilli which have become attenuated, or even completely lost their virulence for rabbits or for guinea pigs may be obtained from some lesions in animals or man, as well as *in vitro*. The niacin test is especially useful for such instances. It distinguished between dysgonic human and eugonic bovine strains, or those which have lost their virulence. Thus a negative niacin test was obtained from cultures isolated from the few cases of fatal disease attributed to BCG, thus confirming the identification which had been originally based on their failure to grow in Besredka's medium.

The vole bacillus, or *M. microti*, is a dysgonic and glycerophobic acid fast bacillus, producing rough white or cream colored colonies resembling those of the bovine tubercle bacillus. Though highly virulent for its original host, the English vole, it is antigenic but does not produce progressive disease in the guinea pig or in man.

The bacillus of fowl tuberculosis, *M. avium*, differs greatly from the mammalian tubercle bacilli of the human, bovine or murine forms. Microscopically it is often thinner and longer than the usual mammalian species,

culturally it appears smoother on solid media and diffuses more readily in liquid, is usually neutral red but not corded, niacin negative, resistant to PAS, amithiazone and isoniazid, as well as to all bacteriophages so far tested, and peroxidase negative but catalase positive, and produces a specific tuberculin different from that of mammalian tuberculin. Only a few instances of tuberculosis due to *M. avium* have yet been reported in man, but it is often found in caseous lesions in hogs, as well as in all kinds of birds, and may also cause disseminated lesions in rabbits.

Acid fast bacilli which may resemble the avian forms, in almost every other way, but which have little or no virulence for birds or rabbits, the so-called "Battey" or type II "atypical" or "anonymous" mycobacteria, have also been found in the sputum or tissues of patients with granulomatous lesions. They are also slow growing, slender acid fast bacilli, yielding smooth discrete colonies, white or cream-colored, often becoming tan when aged rather than from exposure to light, and have similar resistance to tuberculostatic agents as has the avian tubercle bacillus.

Mycobacteria have been obtained from hundreds of species of cold-blooded animals, such as reptiles, amphibia, fish, and even from invertebrates such as snails. They vary greatly in growth rate, pigment production, and other characteristics, as well as in virulence for their original and other hosts. None has been proved pathogenic for man, though some have been reported as causing lesions in some warmblooded, and, more commonly, in coldblooded animals. Many of the poikilothermic mycobacterial cultures in stock collections have lost the properties originally reported for them, and now resemble saprophytes such as *M. smegmatis*, but others retain their distinctive characteristics.

Photochromogenic acid fast bacilli, variously designated as *M. luciflavum*, M. Kansasii, the "yellow" bacillus of Pollak or Group I "Atypical" or "Anonymous" Mycobacteria of Runyan have been repeatedly found in lesions resembling pulmonary tuberculosis as well as in extrapulmonary foci, in patients from whom tubercle bacilli have never been obtained. Though they may resemble tubercle bacilli when grown in the dark, the development of a deep yellow or orange color following incubation in the light, as well as various biochemical and physiological tests show them to be quite different.

Other photochromogenic species of acid fast bacilli may be found in various animals, or in nature, which do not appear to be pathogenic for man. Some of them may resemble *M. luciflavum* but more often they are more rapidly growing, and, like *M. lacticola*, are culturally and physiologically quite distinct.

Some slowly growing acid fast bacteria produce an abundance of bright pigment even when grown in the dark, which may deepen slowly but not change markedly on exposure to light. Some such so-called scotochromogenic parasitic strains, as the yellow producing variety designated as *M. luteum* or *M. scrofulaceum*, have been repeatedly recovered from caseous lymph nodes and other lesions in man and animals, though they do not produce progressive disease in guinea pigs, or mice.

The common orange scotochromogenic or type II species, however, though often encountered in cultures of clinical materials, especially in

gastric lavages, are apparently not pathogenic either for man or animals, and probably represent contaminations as they have been repeatedly found in cultures of dust or of water.

Most rapidly growing cultures, which appear on solid media within a few days after inoculation, have in the past been discarded as contaminants. A number of pathogenic acid fast bacilli have been recognized recently, however, which are also quite rapid in their multiplication.

M. fortuitum, is a rapidly growing non-pigmented acid fast bacillus which has been isolated repeatedly from lesions in man and in animals, and produces a characteristic disease in mice. *M. abscessus*, another rapidly growing non-pigmented mycobacterium found in purulent lesions in man, and animals differ from *M. fortuitum* only in minor cultural and biological characteristics.

Most non-pigmented rapidly growing mycobacteria, which give a smooth, moist, viscous growth may be dismissed as harmless, but others, as some strains of *M. smegmatis* or *M. butyricum* may greatly resemble *M. fortuitum* and require animal inoculation or specific bacteriophage susceptibility tests for their differentiation.

Some poikilothermic mycobacteria are also rapidly growing and photochromogenic, but most of the rapidly growing photochromogenic acid fast bacilli such as *M. lacticola* may be also dismissed as non-pathogens. Although this has also been commonly considered true of the scotochromogenic rapidly growing species, such as *M. phlei* which may appear corded, or the unusual "Radish" bacillus which may be neutral red positive, care must be taken not to miss such pigmented rapidly growing pathogenic varieties as *M. balnei*, or Nocardia.

The vast majority of all acid fast bacteria obtained from clinical specimens are human tubercle bacilli. Most of the rare other strains are readily recognized scotochromogenic saprophytes. A few lesions, however, yield other acid fast bacteria, whose pathogenicity may vary. These may appear relatively insignificant, numerically when compared with the hundredfold more common cases of human tuberculous disease. They present a problem of considerable interest and importance, however, to the individuals concerned.

Recognition of the existence of the scores of different species of acid fast bacilli, including more than a dozen which are capable of producing disease in man, adds greatly to the burdens of the attending physician and of the diagnostic laboratory. The exact diagnosis of the etiological agent concerned, however, is essential if the patients are to receive the benefit of modern chemotherapy, and if the measures, proved effective in the control of tuberculosis are to be extended and adapted to affect the other acid fast bacilli.

SUMMARY

Typical virulent, drug sensitive, human type tubercle bacillus with similar cultural and biochemical characteristics are found in most cases of newly diagnosed pulmonary tuberculosis. Numerous variants in such species appear during the course of chemotherapy, differing in virulence, drug sensitivity, cultural and biochemical characteristics, probably chiefly as a result of spontaneous mutations and artificial selection. There are a number of other species of mycobacteria, quite different from the typical Koch bacillus, however, which may be held to be responsible for human disease. Post mortem bacteriologic and pathologic studies have confirmed their etiologic significance.

Morphologic studies, cultural characteristics, antibiotic and bacteriophage susceptibility, biochemical tests and animal inoculation help to differentiate them from intercurrent saprophytic mycobacteria.

RESUMEN

En la gran mayoría de los casos de tuberculosis diagnosticados como casos nuevos se encuentran bacilos humanos, virulentos, sensibles a las drogas, y con características similares en cuanto la bioquímica y a los cultivos.

Aparecen numerosas variantes de tales especies en el curso de la quimioterapia, con diferencias en la virulencia, la sensibilidad a las drogas, características culturales y bioquímicas, probablemente que como resultado de mutaciones espontáneas y de la selección artificial. Hay cierto número de bacterias sin embargo, muy diferentes del bacilo de Koch típico que pueden considerarse responsables de la enfermedad humana. La bacteriología postmortem y los estudios patológicos han confirmado su significación etiológica. Los estudios morfológicos, las características de los cultivos, la susceptibilidad a los antibióticos y las bacteriófagos, las reacciones químicas y la inoculación de los animales ayudan a diferenciarlos de las micobacterias saprofitas intercurrentes.

RESUME

Dans la plupart des cas de tuberculose pulmonaire récemment diagnostiquée, les auteurs ont trouvé un bacille virulent typique, sensible à la médication, de type humain, avec les mêmes caractéristiques biochimiques et biologiques. De nombreuses variations de ce type apparaissent au cours de la chimiothérapie. Il apparait des différences de virulence, de sensibilité à la médication, des caractères biologiques et biochimiques, résultant probablement de mutations spontanées et de sélection artificielle. Toutefois il existe un certain nombre d'autres types de mycobactéries, assez différentes du bacille de Koch typique, à qui on peut imputer la responsabilité de l'affection humaine. Des études post-mortem bactériologiques et anatomo-pathologiques ont confirmé leur valeur étiologique. Leur étude morphologique, leurs caractères biologiques, leur sensibilité aux antibiotiques et de bactériophage, leurs tests biochimiques et l'inoculation à l'animal permettent de les différencier des simples mycobactéries saprophytes.

ZUSAMMENFASSUNG

Man findet typische virulente, sensible Tuberkelbazillen von typus humanus mit ähnlichen kulturellen und biochemischen Eigenschaften in den meisten Fällen von frisch entdeckten Lungentuberkulosen. Zahlreiche Varianten dieser Spezies treten während des Ablaufes der Chemotherapie auf, Varianten, die voneinander abweichen hinsichtlich ihrer Virulenz, Sensibilität, kulturellen und biochemischen Merkmalen, wahrscheinlich in erster Linie als Ergebnis von spontanen Mutationen und künstlicher Selektion. Es gibt noch eine Zahl anderer Arten von Mycobakterien, die völlig verschieden sin vom typischen Koch Bazillus and trotzdem für die Erkrankung am Menschen verantwortlich gemacht werden können. Bakteriologisch und pathologisch-anatomische Sektionsbefunde haben deren ätiologische Bedeutung bestätigt. Morphologische Untersuchungen, kulturelle Merkmale, Empfänglichkeit gegenüber Antibioticis und Bakteriophagen, biochemische Teste und Tierversuche tragen dazu bei, sie zu differenzieren von interkurrenten saprophytischen Mykobakterien.

Clinical Experience with PZA-INH Therapy: Report on Study of Resected Specimens Following the Above Therapy in Particular

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The clinical effects of pyrazinamide (PZA) and isoniazid (INH) therapy in tuberculosis and experimental studies related to the use of this combined chemotherapeutic regimen have already been frequently reported by numerous investigators. The attention and expectation which have been focused on the use of this combination are, we believe, due to the question of whether its action on tubercle bacilli in the lesions is of an eradicative type as described by McDermott,[1] McCune[2] and Muschenheim[3] and their associates or not, or, if not complete eradicative, whether a more potent bactericidal action is achieved with PZA-INH than with other chemotherapeutic regimens in use at present.

Study of the clinical effects of PZA-INH therapy was carried out in a selected group of patients. In selecting patients for this study we included a number of cases in whom surgical resections were anticipated following the course of treatment, and the resected specimens were examined for the purpose of investigating whether this combined regimen possesses the above mentioned characteristic actions or not.

The clinical results with PZA-INH therapy in our series of patients and pathologic and bacteriologic findings in the resected specimens are presented with discussion of some of the problems encountered with this form of treatment.

Patients Selected for Study and Methods Used

The combination of PZA-INH was administered to 33 patients hospitalized at the Tuberculosis Research Institute of Kyushu University and five other institutes who cooperated in this study.

The age range and sex of the 33 patients are as follows; one was under 20 years, 27 had ages of more than 20 and less than 41 years, 5 were 41 or more years old, and there were 22 male and 11 female patients.

The types of tuberculous lesions before starting treatment included infiltrative caseous form in 15 cases, fibro-caseous forms in 16 cases, and pneumonia with fibrotic shrinkage in 2 cases.

According to WHO's classification, most of the cases were classified into types 4, 6, 8 and 9, which show lesions with apparent cavity in one or both lungs.

When classified according to the N.T.A. classification, 6 were minimal, 20 were moderately advanced, and 7 were far advanced cases.

Before the treatment was started, isoniazid-susceptible strains were found in 17 cases, resistant strains in 11 and the results were uncertain in 5.

The author's clinical standard[4] for drug-resistance was used to judge

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TABLE I—ASSESSMENT OF ROENTGENOGRAPHIC CHANGES

		Improved	Slightly Improved	Unchanged	Worsened	Assessment Impossible	Total
INH Resistance at the Beginning of PZA-INH Therapy	Susceptible	4	5	8(2)*	0	0	17
	Resistant	0	3(3)*	5	2	1	11
	Unknown	0	3	2	0	0	5
TOTAL (per cent)		4(12.1)	11(33.3)	15(45.5)	2(6.1)	1(3.0)	33(100)

*Figures in ( ) are the Number of cases in which therapy was terminated in less than two months.

the susceptibility of tubercle bacilli in this series of patients. Over 1γ/cc 10% or 0.2γ/cc 100% were considered clinically to show resistance to isoniazid.

In all but a few cases where the dosage varied more or less, pyrazinamide, 2 gm, and isoniazid, 0.3 gm, were administered daily.

Treatment was continued for a period of over three months in all the cases except in 5 in whom PZA-INH administration was discontinued after 4 to 8 weeks because of surgical intervention.

Results of Treatment Especially in Regard to Conversion Rate and Closure of Cavities

Numerous observations on the effects of PZA-INH therapy on clinical symptoms and the changes that occur in the results of laboratory tests have been reported. The purpose of this paper is to present a summary of the roentgenographic findings and our observation on the relationship existing between conversion of sputum and closure of cavities.

The roentgenographic changes that occurred during and after treatment are summarized in Table I. Considerable roentgenographic improvement was observed in cases with isoniazid-susceptible bacilli, but the overall rate of cases showing roentgenographic improvement was 45 per cent. The figures in the brackets in Table I show the number of cases that received treatment for periods of less than eight weeks.

In three cases with isoniazid-resistant bacilli that responded favorably to treatment prompt surgical resection was considered the better course and so administration of PZA-INH was interrupted after a short period.

The roentgenographic appearance of cavities in all the cases were examined in detail. Repeated tomograms were taken under as similar a

TABLE II—CHANGE OF CAVITIES IN TOMOGRAMS

		No Cavity from the Beginning	Closed	Reduced in Diameter	Unchanged	Enlarged	Assessment Impossible	Total
INH Resistance at the Beginning of PZA-INH Therapy	Susceptible	1	4	4	6(2)*	1	1	17
	Resistant	0	1(1)*	2(2)*	4	3	1	11
	Unknown	2	0	0	0	1	2	5
TOTAL (per cent)		3(9.0)	5(15.2)	6(18.2)	10(30.3)	5(15.2)	4(12.1)	33(100)
TOTAL (per cent)			5(16.7)	6(20.0)	10(33.3)	5(16.7)	4(12.1)	30(100)

*Figures in ( ) signify the same as those in Table I.

TABLE III—TUBERCLE BACILLI IN SPUTUM, SMEAR

		Negative from the Beginning	Turned to Negative	Remained Positive	Turned to Positive	Total
INH Resistance at the Beginning of PZA-INH Therapy	Susceptible	1	14(1)*	2(1)*	0	17
	Resistant	2(1)*	4(2)*	4	1	11
	Unknown	4	1	0	0	5
TOTAL (per cent)		7(21.2)	19(57.6)	6(18.2)	1(3.0)	33(100)
TOTAL (per cent)			19(73.1)	6(23.1)	1(3.8)	26(100)

*Figures in ( ) signify the same as those in Table I.

condition as possible and the roentgenograms were minutely examined to determine the changes in size of the cavities.

As Table II shows, it was observed that closure or decrease in size of cavities occurred mostly in isoniazid-susceptible cases. In 16.7 per cent of all the cases closure of cavities was observed and this Table increased to 36.1 per cent when cases showing decreases in the size of cavities were included.

On the other hand, comparatively much greater effect on the tubercle bacilli discharged in the sputum was observed. (Table III, IV) In most cases that had conversions of sputum, marked reduction of bacilli in the sputum was noted within several days to several weeks after starting treatment. This observation is similar to that reported by other investigators. Smear examinations were negative for tubercle bacilli in 19 (57.6 per cent) and cultures negative in 18 (54 per cent) of the 33 patients after PZA-INH therapy.

When cases with sputum negative for tubercle bacilli prior to PZA-INH therapy are excluded, 19 (73.1 per cent) of 26 cases had conversions as determined by smear examinations and 18 (64.3 per cent) of 28 as determined by cultures, which are much higher rates than that of closures of cavities.

Study of Resected Specimens

Pathologic and bacteriologic examinations of the resected pulmonary tissues in 15 of the 33 patients in whom lobectomies or segmental resections were performed were carried out. The results are summarized in Table V.

TABLE IV—TUBERCLE BACILLI IN SPUTUM, CULTURE

		Negative from the Beginning	Turned to Negative	Remained Positive	Turned to Positive	Total
INH Resistance at the Beginning of PZA-INH Therapy	Susceptible	1	14(1)*	2(1)*	0	17
	Resistant	1(1)*	2(1)*	7(1)*	1	11
	Unknown	3	2	0	0	5
TOTAL (per cent)		5(15.2)	18(54.5)	9(27.3)	1(3.0)	33(100)
TOTAL (per cent)			18(64.3)	9(32.1)	1(3.6)	28(100)

*Figures in ( ) signify the same as those in Table I.

In three of the 13 patients with demonstrable cavities prior to PZA-INH therapy, roentgenographic evidence of the cavities disappeared after the course of treatment and tubercle bacilli were eradicated from the sputum. The resected specimens in these cases showed closure of the cavity.

In 10 cases that showed roentgenographically persistant cavities after treatment and before operation, six conversions of their sputum and open healing of the cavities was demonstrated on examination of the resected specimens in four of these six cases. Fig. 1, 2, and 3 show respectively the chest roentgenograms, resected specimen and photomicrograph of a section of the cavity wall of Case 1. A section of the cavity wall in

FIG. 1A

FIG. 1B

FIG. 1C

FIG. 1D

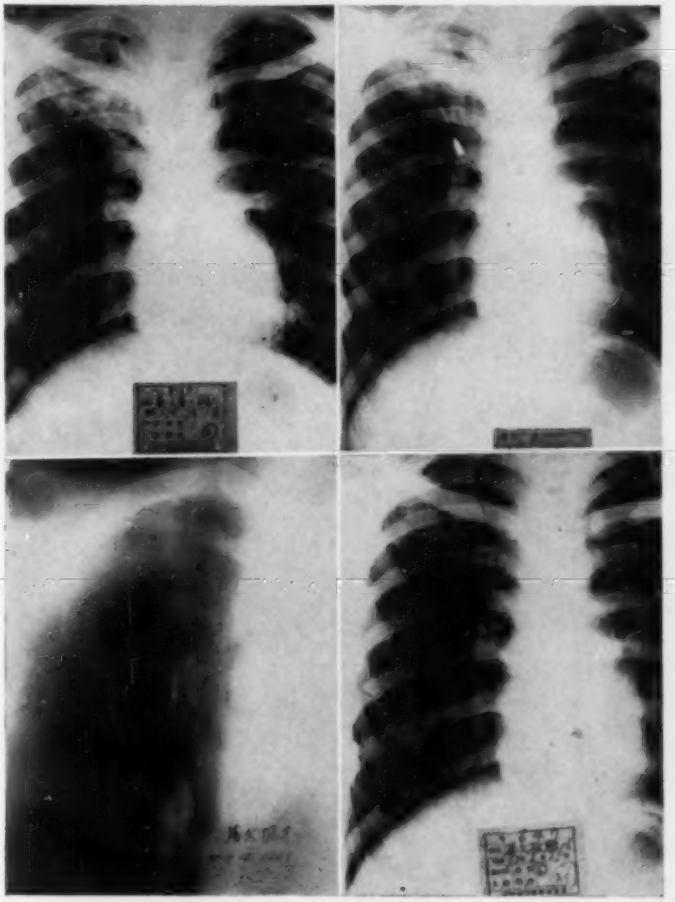

Figure 1 (Serial chest roentgenograms of the patient of case 1): A, Roentgenogram taken on July 13, 1954, before starting combined Streptomycin PAS treatment, shows cavity in the right upper lobe, this regimen was continued until it was changed for PZA-INH regimen.—*Figure 1B:* Roentgenogram taken on March 23, 1955, at the beginning of PZA-INH regimen, shows persistent cavity. There has been clearing of the infiltrate and reduction in size of the cavity caused by the preceding Streptomycin-PAS treatment.—*Figure 1C:* Tomogram of the cavity taken on Nov. 10, 1955, after 5 months of PZA-INH treatment.—*Figure 1D:* Roentgenogram taken June 15, 1956, before the resection of right upper lobe, showing thin-walled cyst-like cavity.

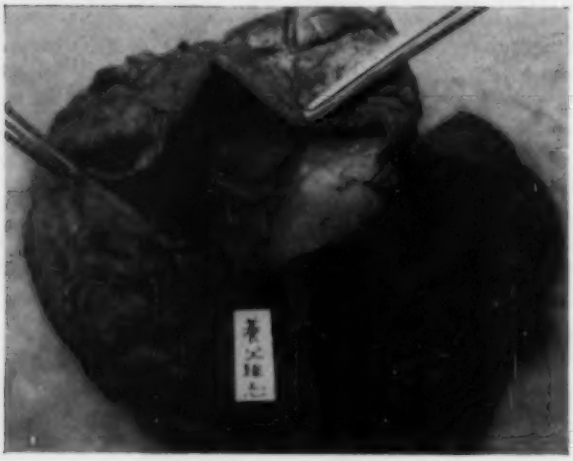

FIGURE 2: Resected specimen in Case 1, shows healed cavity wall.

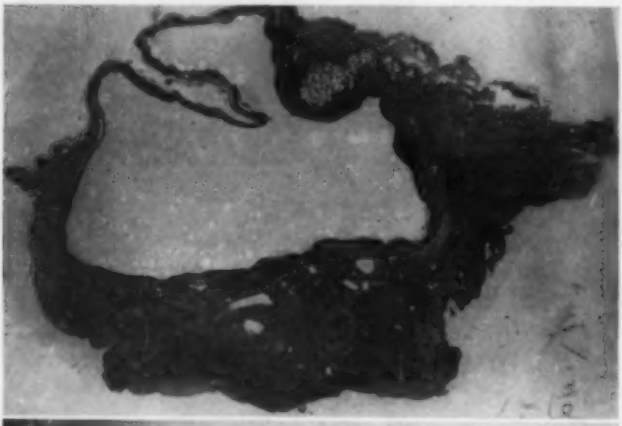

FIG. 3A

FIG. 3B

Figure 3, A and B: Photomicrograph of a section of the cavity wall in resected specimen in Case 1.

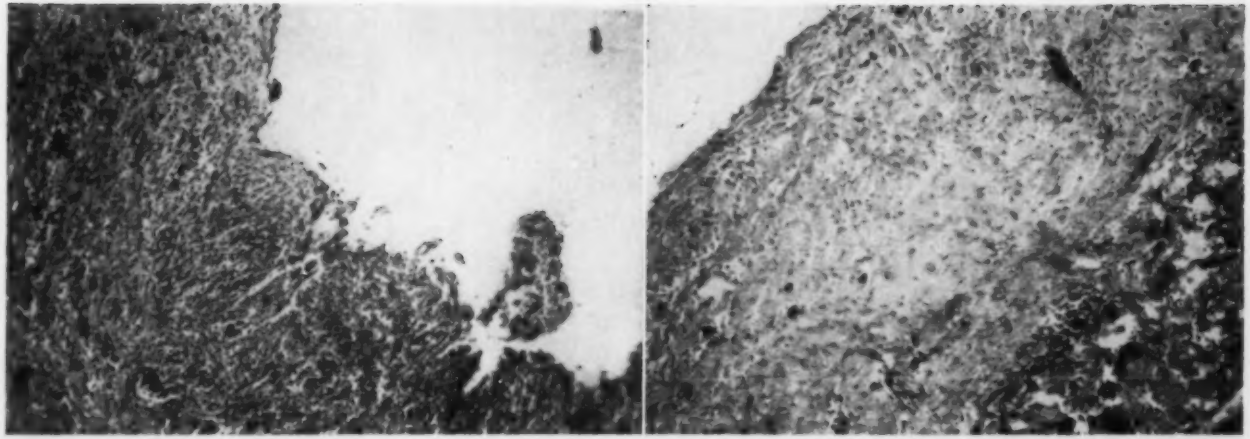

FIGURE 4A FIGURE 4B

Figure 4, A and B: Photomicrograph of a section of the cavity wall in resected specimen in Case 3. In the upper part of Figure 4A, a small portion of inadequate healing of the cavity wall is also shown.

TABLE V—PRE-OPERATIVE ROENTGENOLOGICAL AND BACTERIOLOGICAL FINDINGS AND THE RESULTS OF PATHO-BACTERIOLOGICAL EXAMINATIONS ON RESECTED SPECIMENS IN 15 PATIENTS, WHO RECEIVED EXCISIONAL THERAPY AFTER PZA-INH THERAPY

Case Number	X-ray Findings Existence of Cavity		Sputum Culture			Pathological Findings of Main Lesions in Resected Specimens	Bacteriology in Resected Specimens			Change in Chest X-ray Films*	Duration of PZA-INH Therapy in Months
	At the Beginning of PZA-INH Therapy	Before Resection	Directly Before PZA-INH Therapy	After the Chemotherapy and Before Resection	INH-Resistance at the Beginning of PZA-INH Therapy			Smear	Culture		
1. Y. O.	+	+	+	—	—	Open healed great cavity	1.	—	—	+1	12
2. S. H.	+	+	+	—	—	Open healed cavities	2.	— —	— —	+1	4
3. H. I.	+	+	+	—	—	Encapsulated caseous focus Open healed cavity Bulla	1. 1. 1.	+ — —	— — —	+2	4
4. K. O.	+	+	+	—	—	Open healed cavity Encapsulated caseous focus	1. 1.	— —	— —	0	4
5. I. W.	+	+	+	—		Cavity	1.	?	—	+2	4.5
6. T. A.	+	+	+	—	—	Cavities	2.	— +	+ +	0	1.5
7. Y. A.	+	+	—	+	+	Cavity	1.	+	+	—1	3
8. I. S.	+	+	+	+	+	Cavity	1.	+	+	0	6
9. O. T.	+	+	+	+	+	Cavity	1.	+	+	+1	7
10. I. S.	+	+	+	+	+	Cavity	1.	+	+	+1	1
11. T. E.	+	—	+	—	+	Inspissated cavity Encapsulated caseous foci	1. 2.	+ + +	— — —	+1	1
12. F. U.	+	—	+	—	—	Bulla Inspissated cavity	1. 1.	4	— —	0	4
13. M. A.	+	—	+	—	—	Inspissated cavity	1.	+	—	0	4
14. T. G.	—	—	+	—	—	Lesion changed to radial scar	1.	—	—	0	4
15. H. A.	—	—	—	—	?	A group of encapsulated caseous foci	1.	?	—	+1	5

*+2 Signify moderate improvement.
+1 Slight improvement.
0 No change.
—1 Deterioration.

Case 3 is shown in Fig. 4. In this case, inadequate healing of a portion of the cavity wall is evident. Fig. 5 shows the cavitary lesion in Case 14 replaced by radial scar. Cultures for tubercle bacilli taken from the cavity wall of five open healed cavities were all negative.

In four cases with isoniazid-resistant bacilli conversion of sputum did not occur and the resected pulmonary tissues in these patients showed typical tuberculous cavities with caseous contents.

DISCUSSION

The combination of pyrazinamide and isoniazid administered to our patients was effective in improving the roentgenographic findings in 45 per cent of the cases.

Closure of cavities occurred in 17 per cent, while 70 per cent showed conversion of sputum with smear examinations and 60 per cent with cultures.

We cannot but recognize the fact that since chemotherapeutic agents have come to be extensively used, instances when closure of cavities do not always run parallel with conversion of sputum, that is, instances of roentgenographic cavitary lesions persisting despite absence of tubercle bacilli from the sputum have become increasingly frequent. Nevertheless, the incidence of 60-70 per cent conversions in contrast to roentgenographic closure of cavities in only 17 per cent, as obtained in our study, should be worthy of attention when compared with the results obtained with other currently used antimicrobial regimens.

McDermott and associates[1] were the first to emphasize the fact that tubercle bacilli ceased to be discharged in the sputum for long periods in spite of persisting cavities after PZA-INH therapy, and this observation was statistically demonstrated in clinical cases by Shwartz and Moyer.[5] The latter investigators observed closure of cavities in 29 per cent of their cases and obtained conversions in 83 per cent after four months treatment. Their results coincide closely with those obtained in this study.

Examination of the resected specimens in our series who received excisional therapy following a variable period of PZA-INH treatments revealed open healing of cavities in four of 10 patients that had roentgenographic cavitary lesions preoperatively.

Auerbach[6] has stated that cavity healing with chemotherapy takes the form of inspissation of its contents or replacement by a radial scar and increase in the rate of open healing of cavities.

Bernou and associates[7] observed "cicatrices cavitaires" of less than 3 mm. in 70 per cent of their cases and "cavernes bullenses" or "cavernes sclerocystiques" in 17 per cent after combined treatments with isoniazid and streptomycin or isoniazid and PAS.

Kumagai and co-workers[8] reported marked open healing of cavities in 10 of 105 resected specimens taken from cases with cavitary lesions following combined therapy with streptomycin, PAS and isoniazid.

Thompson[9] examined the resected specimens taken from 240 patients with cavitary lesions and found open healing in 23. The incidence of open healing increased after 1952, as it occurred in 18 of 107 resected specimens between 1952 and 1954, whereas in only 9 of 133 specimens resected before 1952 could open healing be found. This incidence of open healing however is not as high as that reported by Bernou.

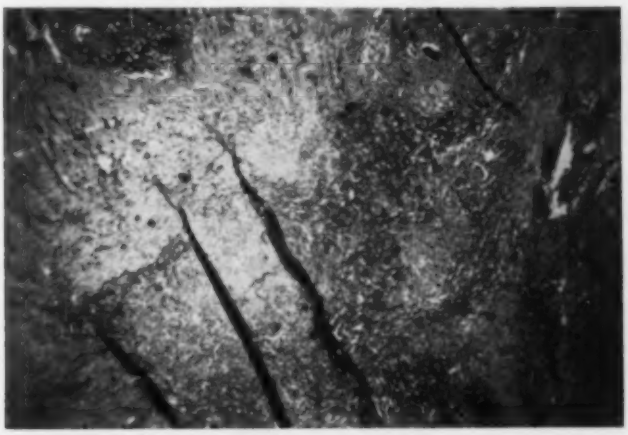

FIGURE 5: Photomicrograph of healed cavity lesion in Case 14 showing radial scar.

Open healing in four of 13 patients with cavitary lesions at the beginning of treatment and in four of 10 who had demonstrable cavities before resection, as observed in our series who underwent surgical resection following combined PZA-INH therapy, should at least be considered a significant finding.

Auerbach and co-workers[10] reported pathologic open healing in 12 of 98 cases with clinically demonstrable cavities before excisional therapy. Streptomycin and PAS were administered to four of their patients and other chemotherapeutic regimens including INH in 8, but as the number of cases was small they reserved their judgement concerning the relation of INH administration to open healing.

In Thompson's 23 cases of open healing, streptomycin or dihydrostreptomycin and PAS were administered to three, and regimens containing INH in 20. As there were no case in their series of patients that did not receive either streptomycin or dihydrostreptomycin, it is impossible to conclude from their results only that open healing is principally related to the use of INH.

However, when we consider the various drugs administered in terms of their duration of treatment before surgery, it is not difficult to speculate on the substantial role played by INH in producing open healing of cavities, as the combination of INH-PAS was given for periods of less than 12 months in most of their cases, whereas streptomycin or dihydrostreptomycin and PAS were mostly used for periods extending over one year.

Johnson and Hewitt[11] observed cyst-like cavities in 22 of their cases, four of which were demonstrated in resected specimens after excisional therapy, and they concluded that the use of INH was specifically related to production of these cyst-like cavities.

Among the French investigators[7, 15-16] who have reported on cases of "caverne bulleuse" or "image bulleuse," Bernou and Bernard regard the use of INH as the predominant factor in their production. Bernard even describing INH as a "médication bullogène." The opinions of these investigators are in accord with those of Kumagai and co-workers, and their opinions viewed together with the chemical casectomy of Purriel and his associates[13] are of considerable interest.

If, as they say, isoniazid plays a prominent role in the resolution and evacuation of the contents in caseous lesions or in open healing of cavities, then judging from the results obtained with our use of PZA-INH, the action of PZA may be considered as intensifying the effects of isoniazid.

Cultures taken from the resected specimens were negative for tubercle bacilli in five of our cavitary cases. In general, positive cultures are obtained in 70 to 80 per cent of resected cavitary lesions. The relatively high incidence of negative cultures (50 per cent) observed in our study could therefore be considered as the apparent outcome of the process of open healing as mentioned above.

It is quite obvious, however, that the state of susceptibility of tubercle bacilli to isoniazid greatly influences the course of the various clinical findings (Table 1 to 4).

As shown in Table 5, of the 10 cases with preoperative cavitary lesions, conversions of sputum occurred in six who had isoniazid susceptible bacilli at the start of the treatments, and four with resistant strains to isoniazid continued to discharge tubercle bacilli in their sputum. Also, open healing of cavities occurred only amoung the six susceptible cases.

As the results of this study show, we were able to demonstrate definite effects of PZA-INH therapy which have not been obtained with hitherto used antituberculous regimens. To decide immediately, however, that these effects were produced by the use of pyrazinamide which was combined with isoniazid is feasible, and it would be more appropriate to consider that the combination of pyrazinamide and isoniazid was directly responsible for producing such effects.

In considering the type of action which PZA-INH exert on the tubercle bacilli, it is our opinion that the descriptive term "eradicative" is unsuitable as a considerable number of infectious cases are still unresponsive to this regimen. Judging from the results of this study, it can be said, however, that compared to other forms of chemotherapy the use of PZA-INH has enlarged the scope of the treatment of tuberculosis.

SUMMARY

PZA-INH therapy was given to 33 patients with pulmonary tuberculous lesions for periods from one to twelve months. In 15 of these, surgical resections were performed following the drugs and the resected specimens were studied. The results were as follows:

1. Roentgenographic improvements were observed in approximately one half of the patients.

2. The incidence of closure of cavities as indicated roentgenographically was 17 per cent, whereas conversions of sputum on smears occurred in approximately 70 per cent and with cultures in approximately 60 per cent.

3. In those who received excisional therapy immediately after receiving PZA-INH treatments, open healing of cavities was observed in four of 10 patients who showed roentgenographic evidence of cavitary lesions preoperatively. Cultures taken from the wall and contents of the cavities in five cases including those with open healed cavities were negative for tubercle bacilli.

RESUMEN

Se dió tratamiento con Pirazinamida e isoniacida a 33 enfermos tuberculosos pulmonares por uno a doce meses. En 15 de éstos se hicieron resecciones después de usarse las drogas y los especímenes quirúrgicos fueron estudiados con los resultados siguientes:

1. Se observó mejoría radiológica aproximadamente en la mitad de los casos.

2. La frecuencia de cierre de cavernas según las radiografías fué de 17 por ciento, en tanto que las conversiones de esputos fué de 70 por ciento en frotis y 60 por ciento en cultivos.

3. En aquéllos que se resecaron in mediatamente después de que se administró PZA-HAIN, la curación abierta se observó en 4 de 10 enfermos que mostraron evidencias de cavidad antes de la operación. Los cultivos de material tomado de las paredes y del contenido de las cavidades en cinco casos incluyendo los de cavernas curadas abiertas fueron negativos para el bacilo de Koch.

RESUME

Une thérapeutique par le PZA-INH fut instituée chez 33 malades atteints de tuberculose pulmonaire pendant des périodes allant de un à 12 mois. Dans 15 de ces cas, des résections chirurgicales furent pratiquées après l'administration des médications et les pièces opératoires furent étudiées. Les résultats sont les suivants:

1. des améliorations radiologiques furent observées dans environ la moitié des malades.

2. le taux de la fermeture des cavités, selon les données radiologiques, fut de 17%, tandis que la négativation de l'éxpectoration sur lames survint dans environ 70% des cas et à la culture dans environ 60%.

3. chez les malades qui subirent un traitement chirurgical immédiatement après l'administration de traitement par le PZA-INH, la guérison des cavités fut observée pour quatre des dix malades, qui avaient présenté des signes radiographiques manifestes de lésions cavitaires avant l'opération. Des cultures faites à partir de prélèvements sur les parois cavitaires et le contenu des cavités dans cinq cas comprenant ceux des guérisons cavitaires furent négatives pour le bacille tuberculeux.

ZUSAMMENFASSUNG

Es erhielten 33 Patienten mit tuberkulösen Lungenbefunden eine PZA-INH-Behandlung während eines Zeitraumes, der zwischen 1 und 12 Monaten schwankte. Bei 15 von ihnen wurden Resektionen vorgenommen im Anschluss an die Chemotherapie und die Resektionspräparate untersucht.

Die Ergebnisse waren folgends:

1. Röntgenologische Besserungen wurden in ungefähr der Hälfte der Fälle beobachtet.

2. Der röntgenologisch festgestellte Cavernenverschluss belief sich auf 17%, wo hingegen Bazillenfreiheit im Ausstrichpräparat in ungefähr 70% vorkam und mit kultureller Bestätigung in ungefähr 60%.

3. Bei denjenigen Kranken, bei denen eine Resektion erfolgte unmittelbar nach der PZA-INH-Behandlung, konnte man eine offene Cavernenheilung bei bis zu 4 von 10 Kranken beobachtet, die vor der Operation röntgenologische Anhaltspunkte für das Bestehen von cavernösen Herden geboten hatten. Kulturen von Material aus der Wand und dem Inhalt von Cavernen bei 5 Patienten einschliesslich solcher mit offener Cavernenheilung blieben Tuberkelbazillenfrei.

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Massive Dose INH in Chronic Resistant Pulmonary Tuberculosis*

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Twenty-two long term patients at Eagleville Sanatorium were treated with massive dose INH plus Pyridoxine HCL for six to 12 months. There were eleven men and eleven women patients, 15 of whom were Caucasian and seven Negro, ranging in age from 28 to 79 years. Sixteen of the 22 were over 45 years of age. All had positive sputum and persistent cavity despite antimicrobial therapy for at least two years. Fourteen had had antimicrobial therapy for five to 10 years. All had been treated with streptomycin, PAS, and INH and the longer term patients had had viomycin, cycloserine[1] and cyanacethydrazide.[2] Resistance to streptomycin was common to all and only three had organisms sensitive to INH prior to large dose therapy. The daily dosage was 20 mg., INH plus 1 mg. pyridoxine HCL per Kg. of body weight in four divided doses. This was given in tablets of 200 mg. INH plus 10 mg. B_6.*** The patients continued streptomycin/PAS. The usual sanatorium regimen was continued. Pneumoperitoneum was continued and surgery was done whenever indicated. Serum assay levels of isoniazid were not done.

Toxicity

All the patients experienced toxic effects initially. Transient tingling and numbness of fingers and toes, giddiness, and lightheadedness was noted commonly. Insomnia was frequent in women and sedation was a common complaint of the men. These effects wore off in a few days or, if severe, the dosage was reduced and then gradually increased as tolerance developed. Peripheral neuropathy occurred in one patient, a Negro of 67 years who received 40 mg. INH per Kg. body weight for three months. This cleared with discontinuance of the drug and parenteral B_6 therapy. The younger tolerated the drug better than the older patients. In a larger series of 41[3] five were unable to tolerate the large dosage. In these five patients dyspnea, tachycardia, somnolence, staggering gait and mental confusion occurred. They were all past 70 years old with marked pulmonary emphysema and cardiovascular complications. There were however no permanent toxic effects, since reducing the dose brought prompt relief.

Clinical Studies

Of the 22 long term patients, 12 showed no change whatever in their clinical course or by x-ray film or sputum studies. It was amazing how little the disease was affected in these chronically ill patients. Progression of the disease was not seen during the period of treatment. Three who

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appeared to hold their own during treatment died four to eight months after the large dose was discontinued. In each case, autopsy revealed acute miliary disease.

Ten patients showed varying degrees of clinical improvement. This was evidenced by weight gain, decrease in cough and expectoration and an increased feeling of well being. There were, however, few significant x-ray film changes. Five of these patients improved sufficiently to tolerate surgery, one of whom turned negative. Three turned negative on the drug regime and have remained so. X-ray film studies of these showed clearing and closure of cavities. In general, the patients who improved were the younger of the group.

Laboratory Studies

Blood, urine, blood chemistry and liver function studies were done routinely and showed no evidence of toxicity. There was no alteration of glucose tolerance or liver function. Most of these chronically ill patients had secondary anemia which was not affected by the therapy. There was no discernible effect on the hemogram, eosinophilia was not seen.

*Guinea Pig Studies**

These were done on 11 patients of the group. All of the animals previously negative became positive reactors to tuberculin. They were sacrificed 60 days after inoculation and at autopsy five animals showed gross lesions of tuberculosis. In the others, there was no gross lesion but histologic studies showed changes suggestive of tuberculosis.

DISCUSSION

These chronically ill patients tolerated well the large dose INH. The low incidence of neurotoxicity does not support the feeling that previous treatment with INH predisposes to neurotoxicity. The protective value of Pyridoxine even in the small dose used is confirmed.[4] The antagonistic effect of B_6 on INH does not appear to be a factor in the view of the small dose used in relation to the large dose of INH. This is evident in the patients that improved and especially in those that converted. It is significant that progression of disease was seen only in one patient during treatment. This was a white man of 55 years who after second stage thoracoplasty showed a new area of contralateral disease. This seems to be clearing with the continuance of the drug. It is interesting that this patient had INH susceptible organisms. One other patient, a woman of 38 showed a contralateral spread to lower lobe following lobectomy and during thoracoplasty. This occurred six months after discontinuance of the large dose regimen. Three patients have died. Two of them had had surgical procedures. Death occurred four to eight months after treatment was discontinued. In each case autopsy revealed acute miliary spread. It appears significant that except in the man undergoing surgery, progression of disease did not occur under treatment and when it did it was long after the drug dose was reduced or discontinued. The question naturally arises as to whether large dose therapy may have prolonged the lives of the patients by delaying the ultimate progession of the disease. It is interesting that the three patients with INH susceptible organisms, continued to discharge INH susceptible organisms in spite of the dose used. Two of the three subsequently converted, one of whom had lobectomy. The improvement noted in the younger patients indicate that exudative disease will respond. Larger dose INH appears indicated in pulmonary tuberculosis especially when serum assay levels cannot be done routinely.

SUMMARY

Twenty mg. INH per Kg. body weight may be safely used in patients with chronic pulmonary tuberculosis. Young persons tolerate the drug better than those who are older. The younger patients having less lung destruction and fibrosis and greater pulmonary reserve appear to benefit. Small doses of B_6 apparently protects against peripheral neuropathy.

*Courtesy of Dr. C. J. Gentzkow, Director of Laboratories, Dept. of Health, State of Pennsylvania.

RESUMEN

La dosis de 20 mg. por kilo de peso, puede usarse con seguridad en los enfermos de tuberculosis pulmonar. Las personas jóvenes toleran la droga mejor que los de edad mayor. Los jóvenes con menos destrucción y fibrosis y con mayor reserva pulmonar parecen beneficiarse.

Pequeñas dosis de vitamina B_6 aparentemente protegen a los enfermos contra la neuropatia periférica.

RESUME

On peut utiliser sans danger 20 mmg. d'isoniazide par kilogramme de poids corporel chez les malades atteints de tuberculose pulmonaire chronique. Les personnes jeunes tolèrent la médication mieux que celles qui sont plus âgées. Les malades jeunes ont une destruction pulmonaire et une fibrose moins importante, et semblent bénéficier d'une plus grande réserve pulmonaire. De petites doses de vitamines B_6 semblent éviter une atteinte nerveuse périphérique.

ZUSAMMENFASSUNG

20mg pro Kilogramm Körpergewicht INH können ohne Gefahr bei Kranken mit chronischer Lungentuberkulose zur Anwendung gelangen. Jüngere Menschen vertragen das Mittel besser als ältere. Die jüngeren Patienten, die geringere Grade von Lungenzerstörungen und Fibrose und eine grössere pulmonale Reserve aufweisen, scheinen im Vorteil. Kleine Dosen von B_6 schützen augenscheinlich gegen periphere Neuropathie.

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Effect of Pneumoperitoneum on the Phagocytosis Enhancing Action of Blood Serum

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Although the pneumoperitoneum (in the following: pnp.) treatment is considered to be an effective and generally accepted therapeutic procedure in pulmonary tuberculosis, the frequency of its use varies not only from country to country, but also from institute to institute in the same country. In Hungary the number of pnp. treatments has increased from 8.5 to 11.2 per cent in the period 1953-56. However, in the bigger pulmonary centers pnp. is employed much more frequently, in about 10 to 30 per cent of cases.[1] Thus, in these institutes pnp. appears to be second only to anti-tuberculosis drugs in the treatment of pulmonary tuberculosis. And if we realize that pnp. is used in an increasing number of non-specific diseases, for example emphysema, its significance will be even more obvious.

In spite of its extensive use, the mode of action of pnp. still awaits full elucidation. The benefit derived from its use in emphysema has been ascribed by Bányai,[2, 3] a universally acknowledged authority on the subject, to the following factors: 1) it raises the diaphragm, 2) abolishes traction by the liver and spleen, 3) the increased intraabdominal pressure relieves reflectorily the peribronchial smooth muscle spasm, 4) intrathoracic pressure is made more negative, 5) the distribution of air in the lungs is improved, 6) through these the O_2 saturation of blood is improved and the CO_2 concentration of blood is lowered, 7) venous back-flow to the heart is improved, 8) the heart ejects more blood into the lungs and, finally, 9) the mechanism of coughing is improved.

However, in infectious diseases, such as tuberculosis, the question emerges whether the use of pnp. *stimulates or inhibits the immunobiological reactions aimed at fighting off the disease.* One of the manifestations of systemic defense is the phagocytosis of bacteria by leukocytes, that is inhibited by some agents and stimulated by others. This stimulation and inhibition can be measured by suitable methods.

Materials and Methods

In order to determine the effect of pnp. on the phagocytotic activity of leukocytes, the phagocytosis enhancing effect of the blood sera from 10 patients with pulmonary tuberculosis has been determined by the method of Ludány and Vajda, before and after pnp.

Fasting blood samples were obtained in the morning for the above test, for making quantitative and differential blood counts, as well as for making eosinophil counts. After that, pnp. treatment was begun by administering 500 ml. of air intraabdominally. Further blood samples were obtained one hour and four hours later. Until the third blood sample had been taken the patients were forbidden to eat, to smoke or to take any drugs. In four

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cases the tests were repeated in the third or fourth week of pnp. treatment, after re-filling with 700 ml. of air. Three women and four men were involved. In two cases the process was apical haematogenic, in two it was fibrocavernous and in the remaining six cases it was infiltrative.

The method employed may be described in brief as follows: To 0.2 ml. of serum in siliconized tubes was added 0.1 ml. of a 24-hour culture of a strain of Staphylococcus pyogenes aureus. One mm.^{3} of the suspension used contained 10,000,000 germs. To this mixture was added 0.2 ml. of a suspension containing 10,000 leukocytes per cu. mm. The leukocytes were obtained by the method of Müller,[4] from heparinized blood of normal subjects of homologous blood group. The mixture was incubated at 37° C. for 30 minutes. After centrifuging, smears were made of the sediment and stained according to May-Grünwald-Giemsa. In each experiment we counted the number of bacteria phagocytosed by 400 leukocytes (limits of error of counting = ± 8 per cent). The results have been summarized in Table I.

The phagocytosis enhancing effect of serum increased in variable degree, (Table I), but in every case following pnp. The average increase was about 35 per cent. This rise resulted not only when pnp. had been made for the first time, but also on re-filling. To elucidate the mode of action in some measure, the results have been compared with those for the eosinophil counts. Crabbé[5] has found namely that following the administration of small doses of cortisone (0.2 mg./Kg. daily) the macrophages of his experimental animals phagocytosed about 50 per cent more of staphylococci than before treatment. Ludány, Vajda and Döklen[6] have shown that in the rabbit small doses of ACTH (0.2 U./Kg.) enhanced the phagocytotic activity of leukocytes. On the other hand, large doses of cortisone caused a temporary decrease in phagocytosis. Ludány, Vajda and Tóth;[7] Ludány, Vajda, Horváth, Tóth;[8] Vajda[8a]).

The more important data for the eosinophil counts and blood counts are presented in Table II.

As the data in Table II reveal, on pnp. treatment, either initial or repeated, the eosinophil count decreased. A comparison of the extreme cases

TABLE I

No. and Initials	Phagocytotic Activity Per Cent Following First Pnp. at 1 Hour	Phagocytotic Activity Per Cent Following First Pnp. at 4 Hours	Phagocytotic Activty Per Cent In 3rd or 4th Week of Pnp., 4 Hours After Re-filling
1. A. A.	+37.7	+35.5	+37.5
2. D. A.	+51.5	+46.0	+35.7
3. H. P.	+40.0	+37.3	+37.8
4. R. I.	+40.1	+34.8	+26.4
5. P. N.	+36.5	+30.0	
6. R. V.	+27.9	+30.2	
7. Sz. J.	+25.0	+36.0	
8. Sch. J.	+28.0	+36.0	
9. N. S.	+40.6	+25.4	
10. Cs. I.	+28.5	+36.5	

(Cases 9, 10, and 3 and 5, respectively) with the extreme cases of phagocytotic activity (Cases 2 and 9, respectively) will show no close parallelism between the two changes. As, however, the tests were made at the same time and were not continuous, it cannot be excluded that a closer parallelism could have been demonstrated in case the tests had been repeated at shorter intervals. The course of systemic reactions may namely show a shift in time. It can be seen also in Table II that in the majority of cases pnp. was followed by a marked increase in leukocyte count (in Cases 1, 2, 4, 5, 7 and 9). In some cases (Cases 1, 2, 4, 6, 7, and 8) there is a remarkable decrease in the lymphocyte count and an increase in the number of polymorphonuclears.

Discussion

In connection with ptx. treatment Kováts, Ludány and Vajda[9] demonstrated that ptx. increased the phagocytosis enhancing effect of serum in man and in animal experiments. This has been ascribed to central-sympathetic excitation. Ample evidence is available to show that ptx. treatment can be considered to be a sympathetic stimulation (Andrus and Wilson, Ceruti and Costa, Puder, Lengyel and Bánát, etc.).

According to the investigations of Kokas, Ludány and Vajda[14] splanchnic stimulation increases the phagocytosis enhancing effect of blood serum. This effect does not develop after adrenalectomy. In man and dog the injection of adrenalin, nor-adrenalin, ephedrine had a similar effect. In effective pnp. Kurbatova[15] found that acetyl-

TABLE II

Number		Percentage Change in Eosinophil Count	Leukocyte Count	Polymorphonuclears Per Cent	Lymphocytes Per Cent
	I.		10,300	62	22
	II.	—50	13,800	84	14
1.	III.		6,700	54	32
	IV.	—74	9,400	68	26
	I.		5,200	54	30
	II.	—60	10,200	86	12
2.	III.		5,000	68	18
	IV.	—26	7,000	78	18
	I.		8,200	68	16
	II.	—22	8,800	60	20
3.	III.		9,000	72	26
	IV.	—11	7,000	76	16
	I.		5,700	60	16
	II.	—63	10,400	80	12
4.	III.		5,900	26	48
	IV.	—28	5,000	44	44
	I.		6,500	58	30
5.	II.	—38	8,700	62	20
	I.		12,900	70	14
6.	II.	—58	13,000	80	10
	I.		5,600	54	36
7.	II.	—52	8,000	72	22
	I.		7,400	56	30
8.	II.	—42	7,400	74	18
	I.		9,000	72	26
9.	II.	—83	11,300	70	22
	I.		6,700	56	26
10.	II.	—68	7,400	66	30

I. before pnp.; II. four hours after pnp.; III. in third or fourth week of pnp., before re-filling; IV. four hours after re-filling.

choline decreased in, or disappeared from blood. This has been suggested to be due to a shift in the sympathetic direction in the tone of the vegetative nervous system. In earlier work Vargha[16, 17] studied the effect of onset of pnp. on the vital capacity in 50 cases and found that the patients responding with an increase in vital capacity to the injection of adrenalin before pnp. responded similarly to pnp. as well. This has been attributed to an adrenalin-effect of pnp. It has been assumed that in these cases both adrenalin and pnp. relieved a latent bronchial spasm and this would have resulted in an increases of vital capacity. Wick[18, 19] has found in animal experiments that the bronchi dilated in response to the mechanical stimulation of the diaphragm in the normal, but not in the splanchnicotomized animals. Thus, also pnp. may cause a dilatation of bronchi, partly by stretching the diaphragm, partly by increasing intraabdominal pressure; the inflated air may cause namely, either reflectorily, or through adrenalin production, a dilatation of bronchi. Le Bec and Bourhis[20] have reported the clinical observation that in their patients with asthma vital capacity increased and the attacks were alleviated on pnp. treatment. This is another evidence indicating that pnp. may act in the sympathetic direction and may cause dilatation of bronchi.

Our present investigations show that pnp. increases the phagocytosis enhancing effect of blood serum, presumably by mobilizing adrenalin as it is indicated by the fall in the eosinophil count. Whether this takes place through an increase in cortisone production caused by adrenalin, it cannot be told at present. The leukocytosis, the increase in the number of polymorphonuclears and the lymphocytopenia may be interpreted as signs of a sympathetic excitation. This enhanced phagocytosis makes it easier for the organism to fight off bacteria. A number of authors have found increased phagocytosis in tuberculosis and have ascribed it to a defensive effort of the body against infection. In general, this increase in phagocytosis is thought to be non-specific, it being elicited by tuberculosis bacilli and other bacteria alike.

Thus, pnp. treatment may have the other favorable effect of diminishing fibrosis and promoting the absorption of inflammatory products, like a mild cortisone treatment, either by mobilizing adrenalin, or by enhancing the production of cortisone. Its beneficial effect in asthma may be due, at least in part, to this.

SUMMARY

1. According to investigations made in 10 patients pneumoperitoneum treatment increases the phagocytosis enhancing effect of serum.

2. Simultaneously, the number of circulating eosinophils decreases significantly. In addition, in the majority of cases leukocytosis, granulocytosis and lymphocytopenia can be demonstrated.

3. The above changes may be ascribed to a shift in the sympathetic direction in the tone of the vegetative nervous system, due presumably to an increased output of adrenalin and/or cortisone.

RESUMEN

1. Según las investigaciones hechas en diez enfermos, el neumoperitoneo aumenta la fagocitosis aumentando el efecto de suero.

2. Al mismo tiempo, el número de eosinófilos circulantes disminuye de manera significativa. Además, en la mayoría de los casos puede demostrarse leucocitosis, granulocitosis y lifocitopenia.

3. Los cambios antes descritos pueden atribuirse a un desplazamiento de la dirección del tono en el sistema nervioso neurovegetativo debido según se presume a una producción mayor de adrenalina y/o cortisona.

RESUME

1. Selon les examens pratiqués chez dix malades, le traitement par le pneumopéritoine accroit la phagocytose en augmentant l'action du sérum.

2. En même temps, le nombre des éosinophiles en circulation décroit d'une façon nette. De plus dans la majorité des cas, on peut mettre en évidence une leucocytose, une granulocytose et une lymphocytopénie.

3. Les altérations ci-dessus peuvent être imputées à un changement dans la direction sympathique, dans le tonus du système nerveux végétatif, probablement du à l'augmentation de la sécrétion d'adrénaline et/ou de cortisone.

ZUSAMMENFASSUNG

1. Auf Grund von Untersuchungen, die bei 10 Kranken gemacht wurden, steigert die Behandlung mit Pneumoperitoneum den die Phagocytose fordernden Effekt des Serums.

2. Gleichzeitig nimmt die Zahl der zirkulierenden Eosinophilen beträchtlich ab. Darüber hinaus kann in der Mehrzahl der Fälle eine Leucocytose, Granulocytose und Lymphocytopenie nachgewiesen werden.

3. Die so beschriebenen Veränderungen können einer Verschiebung in sympatischer Richtung im Tonus des vegetativen Nervensystems zugeordnet werden als Folge vorwiegend eines vermehrten Ausstosses von Adrenalin oder Cortison.

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SECTION ON CARDIOVASCULAR DISEASES

Post Mortem Studies on Coronary Atherosclerosis in One Population Group*

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I. *The Degree of Coronary Atherosclerosis in Sedentary and Physically Active 'Normal' White Males*

In a previous post mortem study on sudden death from coronary artery disease in white males it was noted that individuals in sedentary occupations tended to have their fatal attacks more often at a younger age than those in more physically active occupations.[1] Previously Morris in England had reported that the coronary occlusion attack rate was higher in the sedentary bus drivers as compared to the more active bus ticket collectors.[2] The problem remains as to whether this difference in peak age incidence was based on the possibility that sedentary individuals developed atherosclerosis at a more rapid rate than physically active individuals, or whether other factors not necessarily directly part of the atherosclerotic process were implicated as well. In an attempt to partially clarify some aspects of this problem the degree of coronary atherosclerosis was studied at autopsy in normal white males between the ages of 30 and 60 who died suddenly from traffic or industrial accidents, and in whom verifiable occupational histories were available. The cases were obtained from a population group of consecutive Medical Examiner's autopsies in Westchester County. This is part of a continuing post mortem study on coronary atherosclerosis. The character of this population group has been described in previous reports, as well as the details of the technique of the coronary artery examination and grading.[3] However, in brief the coded hearts were fixed in formalin and the coronary arteries were sectioned at two mm. intervals, examined and graded by the same observer (DMS) throughout the entire study. The hearts were examined and graded without prior knowledge of the sex, age, race, occupation and mode of the death of the cases in question. Only after the grading of the coronary arteries was completed and recorded were these findings then related to the pertinent categories of information.

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Over 150 consecutive hearts from cases of sudden accidental death in white males between the ages of 30 and 60 were examined and divided according to the prior occupations of these deceased individuals. The findings are illustrated in Tables I and II. In Table I the detailed listing of the entire series is presented. In Table II a simplified version in which the average grading within each age group is recorded. It may be observed that there is no difference in the degree of coronary atherosclerosis for the two occupational categories in the various age groups. No difference was noted in either group as a whole in the rate of accretion of coronary atherosclerosis. The spread of the various gradings of coronary artery disease is essentially similar in both groups.

DISCUSSION

Eckstein has demonstrated in dogs that the experimental production of partial coronary occlusion followed by exercise of the animals produces in time greater degrees of intercoronary collateral anastomoses than the same grade of experimental coronary occlusion in the absence of exercise. Milder degrees of experimental coronary occlusion were associated with the development of anastomotic channels only when the dogs were exercised.[4] These collateral channels are anatomically similar to those observed by Baroldi et al in human hearts in individuals who had relative cardiac anoxia.[5] These experimental findings appear to be pertinent to the currently reported study. The tendency for individuals in sedentary occupations to die more often at a younger age from coronary occlusion according to the findings in the study, cannot be adequately explained by significant differences in the degree of coronary atherosclerosis between the sedentary group and those engaged in more physically active occupations. It is therefore necessary to look elsewhere for possible explanations. A partial

TABLE I—COMPARATIVE DEGREE OF CORONARY ATHEROSCLEROSIS IN SEDENTARY AND PHYSICALLY ACTIVE WHITE MALES

	Sedentary				Active			
	No. of Cases with Different Grades of Atherosclerosis							
Age In Years	±	+	++	+++	±	+	++	+++
31-35	7	4	2	0	5	5	2	0
36-40	2	3	2	1	2	2	3	0
41-45	2	5	4	1	3	5	4	2
46-50	1	5	6	4	2	4	4	3
51-55	0	3	6	7	2	3	6	8
56-60	0	4	9	4	0	5	7	7
Total	12	24	29	17	14	24	26	20
		(82)				(84)		

TABLE II—TABLE SHOWING AVERAGE GRADING OF DEGREE OF CORONARY ATHEROSCLEROSIS

31-35	36-40	41-45	46-50	51-55	56-60
0.62 (13)*	1.11 (9)	1.33 (12)	1.81 (16)	2.18 (16)	2.00 (17)
0.75 (12)	1.14 (7)	1.57 (14)	1.70 (13)	2.05 (19)	2.10 (19)

*Figures in parenthesis includes number of cases.

answer may be based on differences in the extent of the collateral circulation available in the myocardium in the more physically active male. It is entirely conceivable that the physical activity as reflected in the type of occupation in combination with the gradual narrowing of the coronary arteries promotes the development of a better collateral circulation so that at any given time the physically active male's myocardium will be in a better position to cope with any sudden or acute disturbance than the sedentary male's myocardium with the same degree of coronary atherosclerosis but in whom the collateral circulation has not developed to the same extent.

Consideration of the mechanism as a possible explanation for the difference in the age specific death rates from sudden coronary occlusion in different occupational groups must be given in any clinical investigation into the various aspects of the problem of prevention or treatment of coronary atherosclerosis. In the clinical evaluation of so-called anti-atherosclerotic agents it would appear to be advisable for comparisons to be made in individuals within the same occupational physical activity grouping. Evaluations of differences in incidence rates of coronary artery disease in different geographical areas and at different periods of times must also take this factor into account. What may be considered differences in amounts of coronary atherosclerosis, may in reality only consist of differences in the state of the collateral circulation and the myocardium. This might be a consequence of differences in the distribution of occupational categories in various areas at different periods of time. Likewise what might be considered in recent times to be an increase in the incidence of coronary atherosclerosis might be to some extent only a reflection of a shift in the nature of the working populatin from heavy physical labor to more sedentary occupations as a result of mechanization and automation.

In prior studies on the same series of autopsies it has been demonstrated that the distribution of the various constitutional body types is not vastly different in the sedentary and more active occupational groups. Therefore this could not be considered as the factor that might influence the conclusions. Definite confirmation of this concept must await careful post mortem coronary arterial injections in which the collateral circulation is quantitatively measured in various age groups of individuals in the different occupational categories.

SUMMARY

In "normal" white males between the ages of 30 and 60 who died suddenly from accidental death there were no significant differences in the degrees of coronary atherosclerosis between those engaged in sedentary occupations and those engaged in physically active occupations.

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II. *The Relative Incidence of Atherosclerotic and Thrombotic Coronary Occlusion in Sudden Death (acute physical exertion, age and sex)*

Physical activity as related to coronary artery disease consists of three distinct aspects; firstly, the relationship of activity or lack of it to the pathogenesis of the atherosclerotic process; secondly, the relationship of physical exertion to the precipitation of the manifestations of acute coronary occlusion; and lastly the effect of activity or lack of it on the function of the myocardium—recently or remotely damaged from pre-existing coronary atherosclerosis with or without occlusion.

There appears to be considerable interrelationship of the factors concerned with blood coagulability and lipid metabolism as these may relate to coronary artery disease. Thus, one finds conflicting ideas concerning the early pathogenesis of the lesion. Among these views are: firstly, that mural vascular fibrin deposit is often regarded as the initial nidus of the atherosclerotic lesion; secondly that repeated intimal hemorrhages are a primary factor, and thirdly there is the more widely held lipid inhibition concept. Heparin is not only involved in blood coagulation, but is also concerned with serum lipid clearance. Fatty meals, on the one hand may be related to altered cholesterol levels and on the other hand may precipitate a post-prandial increase in blood coagulability. It appears that unsaturated fatty acids exert a serum cholesterol lowering effect and also enhance fibrinolytic activity. The question of the relationship of the acute thrombotic episode to the underlying atherosclerosis is obscured by this overlap and is consequently not completely resolved. Sedentary situations are said to promote shorter coagulation times on the one hand; exercise is said to lower cholesterol levels on the other hand. Are there factors independent of the atherosclerotic process which leads to thrombosis in the coronary arteries or is the thrombus merely a complication occurring unpredictably in the course of advanced coronary atherosclerosis? What is the relationship of physical exertion to the precipitation of sudden fatal coronary occlusion whether this be atherosclerotic alone or in combination with an acute thrombosis? In order to study some aspects of these problems, 410 consecutively autopsied cases where death had occurred suddenly from coronary artery disease and where reliable histories were available as to the type of physical activity just prior to the acute fatal episodes were analyzed. These constituted the entire group of autopsies

TABLE I—SEX INCIDENCE AND PHYSICAL ACTIVITY PRIOR TO DEATH IN ATHEROSCLEROTIC AND THROMBOTIC CORONARY OCCLUSION
(410 Autopsied Cases)

Type of Occlusion	No. of Cases	Male	Female	No. of Cases with Physical Activity Prior to Attack
Atherosclerotic	310	277	33 (10.6 per cent)	50 (13 per cent)
Thrombotic	100	90	10 (10 per cent)	17 (17 per cent)
TOTAL	410	367	43	67

TABLE II—AGE DISTRIBUTION OF ATHEROSCLEROTIC AND THROMBOTIC CORONARY OCCLUSION—MALES (364 Autopsied Cases)

Type of Case	Under 39	40-49	50-59	60-69	Over 69
Atherosclerotic Occlusion	35	78	84	58	20
Thrombotic Occlusion	5 (12.5%)	26 (25%)	28 (25%)	24 (34%)	6 (23%)
TOTAL	40	101	112	82	26

in this category in the Medical Examiner's office in Westchester County over a period of 6 years. Most of these were cases of sudden death from coronary artery disease that either did not have any previous medical care or evident symptoms, or had died in a public place without attendance from a physician. Westchester County is a community of 675,000 people, and contains representative small cities, towns, villages, industrial, residential, semirural and suburban areas. With few exceptions these cases were residents of Westchester County.

In each instance all of the major coronary arteries were cross sectioned at 2 mm. intervals throughout their entire lengths. The surface area and state of the atherosclerotic process, the extent of terminal narrowing and the presence of recent or old thrombi were noted, as well as the presence of old and recent myocardial infarcts. Note was made of any evidence of other forms of heart disease. The heart weight was recorded. These findings were related to age, sex and to the type and degree of physical exertion prior to the attack that led to sudden death.

In Table I it may be noted that one out of every four cases had a thrombus. This same ratio persisted when the cases were divided according to sex. Of the 410 cases, 67 had a definite history of physical activity that could be classified as moderate to strenuous in the period immediately preceding the onset of the attack. When this type of physical activity was related to the atherosclerotic and the thrombotic groups no significant differences in incidence were noted.

In Table II the age distribution of the atherosclerotic and thrombotic coronary occlusions in the male group is recorded. In this table it is noted

TABLE III—ATHEROSCLEROTIC AND THROMBOTIC CORONARY OCCLUSION AGE DISTRIBUTION—FEMALES

Type of Case	Under 50	50 and Over
Atherosclerotic Occlusion	7	24
Thrombotic Occlusion	3	9
TOTAL	10	33

TABLE IV—RELATIONSHIP OF TYPE OF OCCLUSION, INFARCTS AND STRENUOUS PHYSICAL ACTIVITY TO ONSET OF SUDDEN FATAL ATTACK (367 Autopsied Males)

	Type of Occlusion	No. and Per Cent of Cases with Infarcts	No. and Per Cent of Cases strenuous Activity	No. and Per Cent of Cases Activity and Infarcts
Atherosclerotic	277	68 (25)	41 (6)*	11 (27)
Thrombotic	90	31 (34)	15 (2)*	8 (53)

*6 and 2 cases respectively engaged in strenous activity in contrast to usual occupational activity.

that under the age of 39, thrombotic occlusion was present in 12.5 per cent of the cases and increased in succeeding decades so that in the age group, 60 to 69 it was 34 per cent. There were insufficient female cases for significant grouping by decades. However, these were divided into two groups with the age 50 as the dividing point. This age was taken as an approximation of the menopausal period. Although the number of cases (43) was too small for a meaningful study, no noteworthy difference in the sclerotic-thrombotic ratio was observed in the two age groups (see Table III).

In Table IV, the incidence of recent and old infarcts in both groups, as well as the relationship to physical exertion prior to the sudden fatal episodes are noted. Again no significant differences between the atherosclerotic and thrombotic groups are observed. Furthermore, moderate to strenuous physical exertion as a possible precipitating factor was no more frequent in the cases with infarcts than in the entire group studied with perhaps one exception. The possible exception is in that group of cases in which thrombosis and infarcts were both present. In this situation over 50 per cent of the cases had a history of previous physical exertion. The number of cases involved in this group is too small for any conclusive interpretation. It is probable in this latter group, because of the nature of the autopsy findings, that the recorded physical activity occurred after the occlusive event rather than prior to it. It is also of interest to note that only very few individuals were engaged in strenuous activity not related to their usual occupational activity.

These findings would favor the concept that coronary thrombosis is a complication that occurs during the course of coronary atherosclerosis and is not an independent process. If independent factors were of primary importance in the development of thrombosis, the occurrence of similar sex distribution and physical activity incidence in the two groups, namely the atherosclerotic and the thrombotic would be unlikely. The age ratio also favors this concept, since one would obviously anticipate an increase in the proportion of thrombotic cases, the longer the sclerotic process existed. The findings in the coronary arteries relative to the atherosclerotic-thrombotic ratio in this group of cases differ considerably from that seen in coronary artery disease in the usual hospital autopsy series where thrombosis super-imposed on atherosclerosis outnumbers those without thrombosis in the cases of death from coronary artery disease. The one obvious difference between the Medical Examiner's cases and the hospital cases, is the time element between the onset of the attack and death. Those in the hospital had a longer interval between the onset of the acute attack and death. Does this perhaps signify that a thrombus may develop in some cases secondary to a pathophysiological disturbance in rhythm, blood flow or a functional occlusive event rather than be a precipitating factor? Although this study was not designed with the technique and care necessary for the exact evaluation of intimal or mural hemorrhages as a factor related to thrombus formation, gross intimal or mural hemorrhages were seen only on occasion in the atherosclerotic group in which no thrombi were present.

SUMMARY

1. Strenuous physical activity, or exertion prior to sudden death from acute coronary artery disease, occurs less frequently than one would expect even as a coincidence

and does not appear to be a factor of any significant consequence except in the occasional case. This relationship or lack of it to physical exertion is the same for both the atherosclerotic and thrombotic types of occlusion.

2. The findings in the report support the concept that acute coronary thrombosis is primarily a complication of, and intimately related to, the atherosclerotic process rather than being primarily related to other independent factors.

III. *Degrees of Aortic Atherosclerosis as Compared to Coronary Atherosclerosis—Sex and Age Differences*

One of the perplexing problems concerning the pathogenesis of atherosclerosis is the variable degree of involvement of different arteries not only within the same individual but in different geographical population groups. In the same individual there may be extensive coronary atherosclerosis with only minimal involvement of the aorta and/or cerebral vessels; all may be involved extensively; or the cerebral vessels or aorta may have considerable involvement and the coronary arteries may only show minimal changes. Likewise group differences exist as for instance in Japan where cerebral arterial disease is relatively common and advanced coronary atherosclerosis is relatively uncommon. It has also been established in this area that coronary atherosclerosis as a cause of sudden death in the nonhypertensive and non-diabetic white female under the age 50 occurs at a rate of only 5 to 10 per cent of that in comparable males. It therefore is pertinent to determine whether the sex differences that exist for the degree of coronary atherosclerosis extend to aortic atherosclerosis and whether this is altered over the age of 50 (menopausal age). A study was instituted in which the comparative degree of aortic and coronary atherosclerosis in the same individuals were analyzed in both sexes. The autopsy material was obtained from the same source as that in other sections of this report. The same methods were used for examination and the aortas were graded independently of the coronary arteries without prior knowledge of the age or sex of the cases in question. The cases were then divided into three groups. Those in which the aorta had a lesser grading for atherosclerosis than the coronary arteries, those in which there was an equivalent grading, and those in which the aorta had a higher grading for atherosclerosis than the coronary arteries. The cases were grouped according to sex and into two age categories 30-50 and 50-70. The age of 50 was chosen as a dividing point to approximate the female menopausal period. The findings are listed in Tables I and II. Under the age of 50 in males and females the gradings for atherosclerosis in the coronary arteries did not correspond to that in the aorta in 60 per cent of the cases. In the female in approximately one half of the cases the aorta had a higher grading than the coronary arteries. In only 13 per cent did the coronary arteries show a greater grading for atherosclerosis than the aorta. In the male the situation was reversed. Only 8 per cent of the males had a lesser grading in the aorta than the coronary arteries, whereas in 60 per cent the coronary arteries revealed a higher grading than the aorta. Over the age of 50 the pattern of the relative gradings of the coronary atherosclerosis in the female tended to approach that noted in the male. The entire picture tended to level off so that the distribution of the relative relationships of coronary to aortic atherosclerosis

TABLE I—RELATIVE DEGREE OF ATHEROSCLEROSIS IN AORTA AND CORONARIES (Between 30-50 Years of Age)

	Aorta Coronary	Aorta Coronary	Aorta Coronary
Female (46 cases)	21 (46 per cent)	19 (41 per cent)	6 (13 per cent)
Male (77 cases)	6 (8 per cent)	25 (32 per cent)	46 (60 per cent)

TABLE H—RELATIVE DEGREE OF ATHEROSCLEROSIS IN AORTA AND CORONARY ARTERIES (Between 50-70 Years of Age)

	Aorta Coronary	Aorta Coronary	Aorta Coronary
Female (43 cases)	14 (33 per cent)	17 (40 per cent)	12 (27 per cent)
Male (89 cases)	24 (27 per cent)	28 (30 per cent)	37 (43 per cent)

was almost equally divided in the three groups. Although it is not indicated in the table the general degree of atherosclerosis in the aorta in the female was only slightly less than that in the male, whereas the differences in the degree of coronary atherosclerosis under the age of 50 were marked.

DISCUSSION

Stamler and his associates[1] in their experiments on the production of atherosclerosis in chickens were able with estrogens to prevent or reverse induced atherosclerosis in the coronary arteries but not in the aorta. This indicates that in this respect at least the human situation may be similar to that seen in the chicken to the extent that estrogens are a factor in the atherogenic process, and there may be a more specific relationship to coronary atherosclerosis than to aortic atherosclerosis. The general differences as well as the specific sex differences in the relationship between the amount of atherosclerosis in the aortic and coronary arteries may also indicate that certain local vascular factors (humoral, enzymatic and/or hemodynamic) may be important in determining the differential rate of atherogenesis.

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IV. *Coronary Atherosclerosis in White Male Suicides*

There is much speculation concerning the role of stress in the complex maze of factors involved in the pathogenesis of atherosclerosis. Speculation is plentiful but verifiable facts are scant. There is not only a lack of agreement as to what constitutes stress, but also in the means of measuring stressful situations and the individual's reaction to them. At present there is no readily available body of data on this subject that can be applied in a meaningful way to the problem of atherosclerosis. In order to begin at least a feeble and simple approach to the problem that would at least yield measurable data, a post mortem analysis of the degree of atherosclerosis in coronary arteries of non-institutionalized white males who had committed suicide was made. This group was compared with the degree of

coronary atherosclerosis in a comparable age group of males from the same community who had died suddenly as a result of accident. The cases were all consecutive ones that had been autopsied in the Medical Examiner's office of Westchester County. In this type of study the degree of coronary atherosclerosis could be measured and compared, and suicide was a clear end-point indicator of severe emotional disturbance. Non-institutionalized suicides were selected because the general environment, habits, occupational activities and diet would more closely approach that of the control group of individuals. The distribution of constitutional body types and occupational activities of the two groups was not sufficiently different to render the results invalid. In this study 50 consecutive suicides

TABLE I—50 WHITE MALES (Sudden Death from Accidental or Traffic Accident)
GRADE OF CORONARY ATHEROSCLEROSIS

Age	±	+	++	+++	Totals
25-36	3	4	2	0	9
36-40	1	4	1	1	7
41-45		3	3	2	8
46-50	1	2	2	4	9
51-56	0	1	2	2	5
56-60	0	1	2	1	4
61-65	0	1	1	2	4
Over 65	0	0	1	3	4
TOTALS	5	16	14	15	50

TABLE II—50 WHITE MALE (Non-Institutional) SUICIDES
GRADE OF CORONARY ATHEROSCLEROSIS

Age	±	+	++	+++	Totals
25-36	2	4	1	0	7
36-40	2	3	1	1	7
41-45	1	3	2	2	8
46-50	1	3	3	3	10
51-56	1	2	1	1	5
56-60	0	1	1	2	4
61-65	0	0	2	2	4
Over 65	0	0	1	4	5
TOTALS	7	16	12	15	50

were compared with 50 accidental deaths. Apparent suicides and apparent accidental deaths were omitted if the coronary atherosclerosis was present to such a degree that this might have been the cause of what on the surface appeared to be suicide or accident. These were very few in number. Some degree of selection was necessary in the accidental deaths in order to assure an age group comparable to that of the suicides. It will be noted in Tables I and II that in the various age groups studied there were no significant differences in the distribution of the degree of coronary atherosclerosis.

SUMMARY

An obviously limited study was made on a group of suicides in Westchester County who were undoubtedly emotionally disturbed individuals and who had responded in the most extreme manner to stressful life situations. At the various age levels studied there was no difference in the degree of coronary atherosclerosis from the control group of white men who died from accidental death. These findings of course bear no relationship to another problem, namely, the effect of overwhelming stressful psychological situations on the precipitation of acute episodes of coronary occlusion in individuals with underlying advanced coronary atherosclerosis. This also is an unsolved problem.

RESUMEN

Se hizo un estudio, que se admite es limitado, en un grupo de suicidas del Condado de Westchester en individuos indudablemente perturbados emocionalmente y que han reaccionada de manera extremada a las circunstancias difíciles en su vida.

En las diferentes etapas de su edad no había diferencia en el grado de ateroesclerosis coronaria en comparación con el grupo de control de hombres de raza blanca muertos accidentalmente. Estos hallazgos por supuesto que no tienen relación con otro problema como es el efecto de las situaciones psicológicas subyugantes en la precipitación de los episodios agudos de oclusión coronaria en individuos con ateroesclerosis coronaria avanzada. Este es también un problema no resuelto.

RESUME

Une étude évidemment limitée a été effectuée sur un groupe de suicides dans le Comté de Westchester. Il s'agissait sans aucun doute d'indivdus affectivement déséquilibrés et qui avaient répondu de la façon la plus extreme aux situations désespérées de la vie. Selon les différents âges envisagés, il n'y eut aucune différence dans le degré de l'atteinte d'athérosclérose coronarienne, d'après le groupe témoin d'individus de race blanche, qui moururent de mort accidentelle. Ces constatations, bien entendu, sont sans relations avec un autre problème, celui de l'effet de situations psychologiques dramatiques accablantes sur la soudaineté des épisodes aigus d'occlusion coronarienne chez des individus atteints d'athérosclérose coronarienne avancée latente. Ceci aussi est un problème qui n'a pas été résolu.

ZUSAMMENFASSUNG

Bericht über eine klar abgegrenzte Untersuchung einer Gruppe von Selbstmorden im Kreis Westchester, bei der es sich zweifellos um Individuen mit Gemütsstörungen handelt, die in äusserst extremer Art auf schwer-belastende Lebenslagen reagiert hatten. Bei den Untersuchungen der verschiedenen Altersstufen fand sich kein Unterschied hinsichtlich des Ausmasses der Arteriosklerose gegenüber der Vergleichsgruppe von weissen Männern, die an einem Unfall verstorben waren. Diese Befunde haben selbstverständlich keine Beziehung zu einem anderen Problem, nämlich der Auswirkung von übermässig stark erregenden, sehr belastenden psychologischen Situationen auf das jähe Zustandekommen akuter Anfälle von Kranzaderverschluss bei Menschen, bei denen eine fortgeschrittene Arteriosklerose besteht. Auch dies ist ein ungelöstes Problem.

The Electrocardiogram and Vectorcardiogram in Right Ventricular Hypertrophy and Right Bundle Branch Block*

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It is the purpose of this paper to appraise certain applications of the electrocardiogram and vectorcardiogram to the diagnosis of right ventricular hypertrophy. The problems that are encountered in this area of electrocardiography are created by the similarity of the records seen in recognizable right ventricular hypertrophy to those that occur in normal infants and to those that are seen in right bundle branch block. The not infrequent failure of any kind of record of the cardiac potentials to reveal recognizable evidence of right ventricular hypertrophy when in fact it is proved to exist adds further confusion to this constellation of difficulties. For the purpose of this paper it has been deemed practical to ignore almost completely problems created by the coexistence of left ventricular hypertrophy and other conditions occurring frequently in rheumatic heart disease (which contribute to the difficulties that are encountered in this area of electrocardiography and vectorcardiography).

Our material consists of 1) serial observations on a large group of normal infants some of whom are now five years of age; 2) observations of individuals with congenital heart disease; 3) observations of normal young adults; and 4) observations on an individual with varying degrees of right bundle branch block. In addition we have reviewed observations of other authors that fall in the first three of the above categories.

At the outset it is necessary to clarify certain matters that frequently appear to become confused in the literature. *In the individual case* entirely satisfactory proof of the presence of right ventricular hypertrophy can be obtained only at autopsy. The inference that the right ventricle is hypertrophied when the intraventricular pressure is high and more especially, the inference that it is not hypertrophied when the intraventricular pressure is normal, must be rejected because of the lack of close correlation between the level of the intraventricular pressure and the degree of hypertrophy found at autopsy in individual cases. On the other hand, when one encounters *a large group of cases* of the same cardiac condition in which a characteristic electrocardiogram is observed, it is not illogical to relate the electrocardiographic findings in question to the presence of that condition. However, the mechanism by which the cardiac condition produces the characteristic electrocardiographic changes may still be open to question. The form of the electrocardiogram may depend upon alterations of the cardiac potentials due to such a structural change as right ventricular hypertrophy or, on the other hand, it may result from a func-

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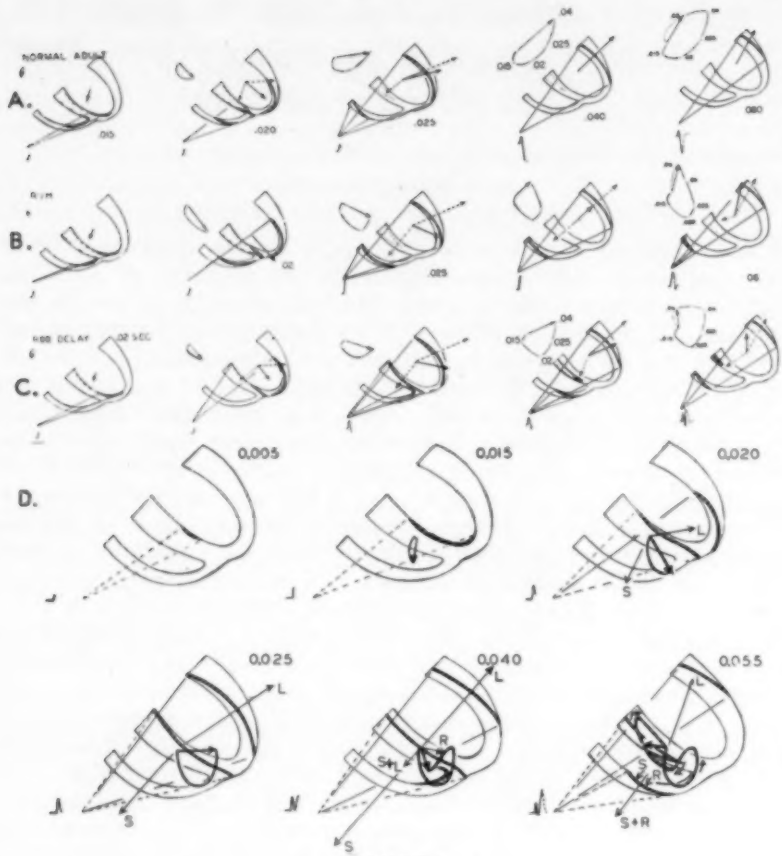

FIGURE 1

Figure 1A: The diagrams represent horizontal sections through a transverse heart that is not rotated about the anatomic axis (intermediate rotation) so that the back is at the top and the anterior chest wall is below. The heavy lines are the waves of excitation.

Five stages in the normal activation of the ventricles are represented. In these diagrams the portions of the waves of excitation in the septum are ignored for it is assumed, insofar as external electrical effects are concerned, that they approximately neutralize one another. For each stage, vectors representing the electromotive force produced by the wave of excitation of the two ventricles are added (vectorially) to obtain the resultant (solid line vector) which shows the direction and relative magnitude of the electromotive force produced at that stage of activation for the whole heart. The path described by the tips of the resultant vectors as we move from stage to stage is the spatial QRS loop, which, with the heart in the transverse non-rotated position shown is also the horizontal QRS loop as it might be recorded with an oscilloscope. Note that the vectors that account for the long axis of the loop result from relatively unopposed excitation in the lateral wall of the left ventricle.

For each of the five stages the potentials recorded at V_1 is estimated by the solid angle method (for electrodes close to the heart single dipole representation cannot be employed).

Figure 1B: Five stages in the activation of the ventricles in the presence of right ventricular hypertrophy of moderate degree. Note that the greater thickness of the right ventricle accounts for the presence of large waves of excitation in the right ventricle at 0.025, 0.040 and 0.060 second than are seen in the normal heart (A) at the same times. These larger waves of excitation must be represented by larger vectors. The increased opposition thus offered to the vectors that normally occur at the same times in the left ventricle accounts for the shortening of the resultant vectors that occur at the respective times.

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tional alteration such as right bundle branch block (or a combination of both). Furthermore, dilatation of the right ventricle and enlargement of the heart may diminish the distance between the surface of the right ventricle and the anterior chest wall and thus cause distortion in the records (due to eccentricity-contour effects) that are, at least in part, of extracardiac origin. It is at least conceivable that some peculiarity of the shape of the torso may have a similar distorting effect upon the records even in the absence of structural or functional change in the heart. It is important to point out that autopsy material is valueless for determining the presence of conduction disturbances and is next to useless in estimating the effects of the contour-eccentricity factors. Under these circumstances the possible roles played by right ventricular hypertrophy, by conduction disturbances, and by the contour-eccentricity effects in the production of the surface potentials recorded must be approached on a theoretic basis.

Theoretic Basis

For this purpose we apply to the analysis of the surface potentials recorded (in the normal) the concept of the path of ventricular excitation (Figure 1A) that we have shown correlates well with the bulk of electrocardiographic data and which has been largely corroborated by the recent experimental findings of Scher[1] and of Durrer.[2] Minor differences between our concept and the findings of Scher in the dog will be recognized at the proper time. Adhering for the moment to the simplest possible assumptions we postulate that when the right ventricle becomes thicker than normal more time is required for the excitatory process to reach the epicardial surface. Thus, if the rate of spread of the process of excitation through the right bundle branch and the Purkinje network in the endocardial surface of the right ventricle is not altered and if no change occurs in conduction in the right ventricular muscle itself then it is to be expected that the waves of excitation in the right ventricle will be larger during most of the process of excitation and will persist longer than in the normal (Figure 1B). Since in most instances the apex of the right ventricle thickens less than the other portions the foregoing statement applies particularly to those waves of excitation that occur after the first 0.02 second. Right bundle branch conduction disturbances are represented by means of the same hypothesis (Figure 1C). This is justified by the recent findings of Scher[3] in experimental right bundle branch block. The existence

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Also because of the occurrence of these large waves of excitation in the right ventricle after 0.02 second, the positive solid angle subtended at V1 is greater than the negative solid angle to the margins of waves of excitation in the left ventricle, and the QRS complex has the form shown.

Figure 1C: Five stages in the activation of the ventricles when conduction in the right bundle branch is delayed by 0.02 second.

Note that there are now important unbalanced effects in the septum and that alone (0.025 second) and combined with the effects of late activation of the right ventricle (0.04 second), these unbalanced septal effects furnish opposition to the left ventricular effects that are similar to those furnished by the larger waves of excitation in the right ventricular wall when the latter is hypertrophied (Figure 1B).

Figure 1D: Six stages of the activation of the ventricles with 0.035 second delay in conduction in the right bundle branch. Whether the loop passes in front of or behind the origin at about 0.40 second depends upon the angle between the vectors S and L and this in turn conceivably depends upon the shape of the individual heart (as shown for complete right bundle branch block, Figure 5). Complicating left ventricular hypertrophy might also be expected to continue the loop to the left and backward if the basal margin of the left ventricle is incurved rather than flared.

of various degrees of right bundle branch delay is accepted on the basis of a wealth of experimental and clinical evidence. Slowing of conduction of the excitatory process in the hypertrophied right ventricular wall is not postulated because there is no experimental evidence and because as hypothesis it departs from the simplest possible assumptions. Slowing of conduction in the right ventricular muscle has been observed by Scher[3] in experimental right bundle branch block in dogs but this finding will require corroboration for the phenomenon may have resulted from trauma involved in the experimental conditions.

Analysis of the Electrocardiogram and Vectorcardiogram in Normal Infants

In normal infants we have the largest available group of individuals whose electrocardiograms and vectorcardiograms show the characteristics in which we are presently interested and in whom the architecture of the heart is well known as a result of autopsy studies.[4, 5] Thus data derived from a study of normal infants furnishes the best available point of departure for an attempt to understand the phenomena with which this paper is concerned. At birth the right ventricle is of about the same thickness as the left and generally the electrocardiogram shows marked right axis deviation in the limb leads and the right precordial leads show large R waves. If we are to attempt to correlate the electrocardiographic findings in these infants with the architecture of the heart, we must employ the theoretic approach depicted in Figure 1B for right ventricular hypertrophy. The findings in the precordial leads can be understood in terms of the solid angle approach. The electrode in the V_1 position is in such proximity to the waves of excitation in the right ventricle that the positive solid angle subtended by the electrode at V_1 is greater than the negative solid angle to the larger wave of excitation in the left ventricle. Thus, records made at V_1 exaggerate the right ventricular effects if interpreted on the basis of single dipole representation. Were single dipole representation applicable the QRS complex could not have the appearance shown for the summation of the vectors representing the right and left ventricular effects, e.g., at 0.04 second (Figure 1B) in infants produces a vector that points away from the electrode; the potential at V_1 should have been negative at 0.04 second and an S should have been inscribed at this time. It is to be remembered that all timing for normal infants is little more than half that for adults.

If we examine the frontal plane leads (I, II, III, AVR, AVL, and AVF) of newborns we frequently find that they either cannot be derived from the spatial loop developed in Figure 1B at all or only by rotating the anatomic axis in a clockwise manner to an exaggerated degree. Studies of the effects of dipole location upon the limb leads in the model torso[6] and even in an infinite medium[7] strongly suggest that the anterior position of the dipoles of the waves of excitation in the right ventricle results in exaggeration of the right ventricular effects and that the posterior position of the dipoles of the waves of excitation in the left ventricle results in a relative diminution of the left ventricular effects. We submit that single dipole representation frequently does not hold even approximately for the limb leads in young infants.

When vectorcardiographic records are made on young infants employing the cube frame of reference we find that the horizontal loop is fre-

quently inscribed in a clockwise manner.[8] According to the theoretic analysis presented in Figure 1B this finding can be expected only if the right ventricle is thicker than the left, Figure 2, a condition that does not generally exist even at birth. Under all of the conditions postulated (including absence of conduction disturbances) we find it difficult to escape the conclusion that the clockwise inscription of the loop in young infants results from distortion inherent in the method of recording. As in the conventional leads this distortion may be described as an exaggeration of the right ventricular effects. Since it depends upon the size and shape of the heart and its position in the torso this distortion may be expected to vary from individual to individual and in the same individual with respiration, as indeed it does.[8] If the respiratory variation is due to "rotation" of the heart then it is analagous to the exaggeration of electrical rotation that we found for the conventional limb leads for it is impossible to subscribe to the notion that the left ventricle ever faces forward in these infants.

It becomes apparent that for the young infant the errors of the cube are in general similar to those of the conventional leads. During the first few months of life the relative thickness of the right and left ventricles approaches more closely the adult proportions though the rate at which this occurs is subject to much individual variation. Our observations indicate that a corresponding evolution of changes is seen in the conventional leads and in vectorcardiograms recorded with the cube frame of reference. Furthermore, the errors common to the conventional leads and the cube method of vectorcardiography make it possible to correlate the findings in the two systems so that a table can be constructed that makes it possible to

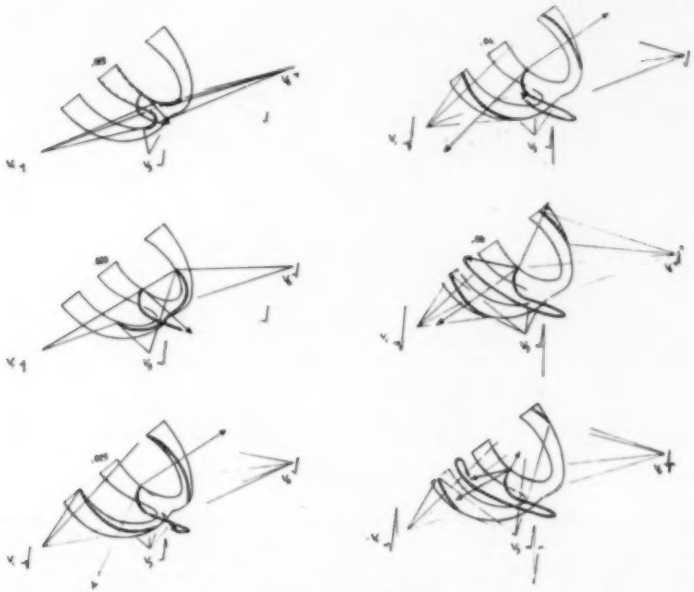

FIGURE 2: Theoretic construction of the QRS loop and QRS complex of Lead V1 showing that (without right bundle branch delay) the loop cannot be inscribed in a clockwise manner unless the right ventricle is thicker than the left.

predict the form of the horizontal loop of the cube method by examination of the conventional leads of the electrocardiogram of infants.[8] The errors in the predictions are no greater than the respiratory variations observed in the same individual. The significance of this correlation must be considered in relation to the allegation that the horizontal loop of the cube is superior to the conventional leads in the recognition of right ventricular hypertrophy. While the correlation itself has no relation to the presence

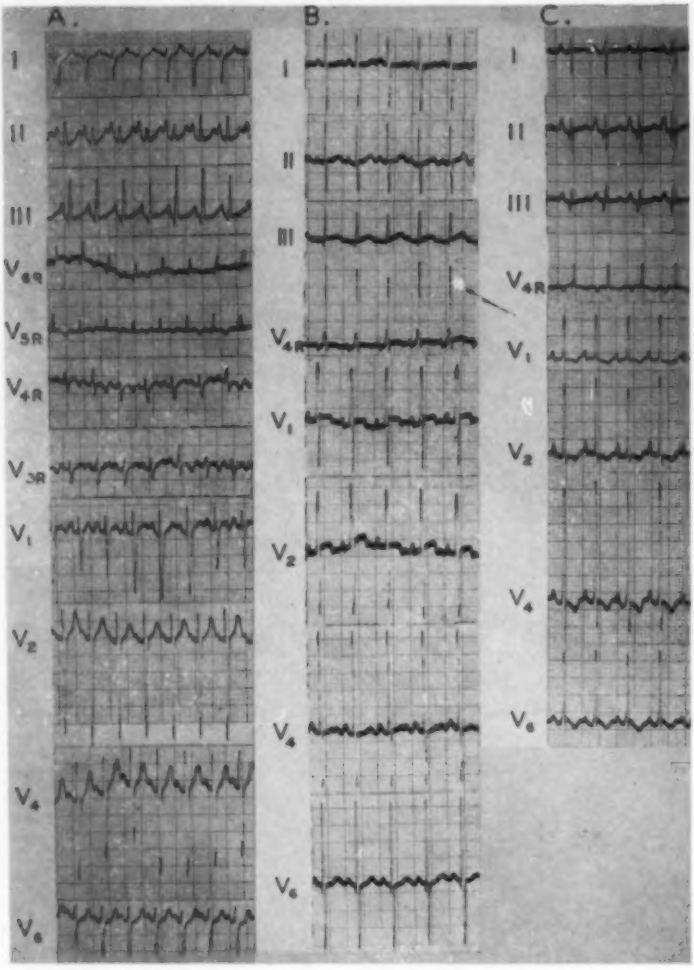

FIGURE 3: The electrocardiogram indicating the presence of right ventricular hypertrophy.

A. There is a marked right axis deviation in the limb leads but all of the conventional precordial leads are characterized by a small R and a deep S wave. Only when the electrode is moved to the V_{6R} or V_{5R} position is the QRS complex represented largely by a positive deflection. B. An exaggerated form of the usual early infantile electrocardiogram. There is a marked right axis deviation with large QRS complexes in the limb leads, a very high R in Lead V_{4R} and a deep S wave in V_6. C. There is marked right axis deviation in the limb leads as in A and a large R in Lead V_1 but the other precordial leads show large R waves and very small or no S waves.

or absence of right ventricular hypertrophy, it is important to point out that the architecture of the ventricles and the electrocardiographic findings in very young infants are similar to those that are encountered in many cases of congenital heart disease with hypertrophy of the right ventricle.

The great variation seen in the rate at which the serial electrocardiograms and the vectorcardiograms evolve in different infants makes it difficult at this time to establish limits for the normal period required for such evolution. Obviously if such a limit could be established, the persistence of the infantile form for a longer period of time than that limit would mean pathologic rather than non-pathologic relative right ventricular hypertrophy. It should be mentioned here that it is at least conceivable that the serial change in the form of the records that is seen during the first few months of life depends not only upon the intrinsic changes that are occurring in the architecture of the heart but also upon the changing relation of the size of the heart to the size and shape of the torso.

The Electrocardiogram and the Vectorcardiogram in Congenital Heart Disease

Since in isolated pulmonary stenosis there is a relative thickening of the right ventricle and there is no hypertrophy of the left ventricle to complicate

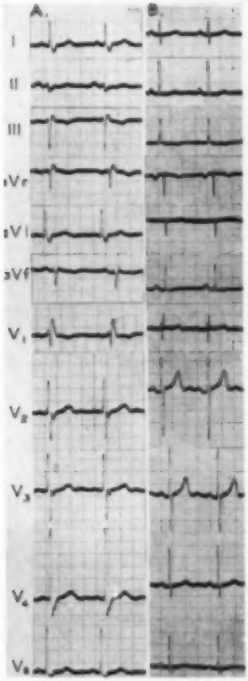

FIGURE 4: Electrocardiograms demonstrating the similarity of the precordial leads in complete right bundle branch block (A) to those of right ventricular hypertrophy (B). The sole difference is in the time required for the inscription of the R' in V_1 and the S in V_5 and V_6. There is no clinical evidence to suggest right ventricular hypertrophy in patient A; patient B has isolated pulmonic stenosis with marked right ventricular enlargement on X-Ray.

the picture it is in this group of individuals with congenital heart disease that the heart is architecturally most similar to that of the young infant. When the records of a large group of these individuals are studied a wide range of variations in the appearance of the electrocardiogram and of the vectorcardiogram is observed. In most cases, however, the records have the form shown in Figure 3. The similarity to the early infantile electro-

FIGURE 5A

FIGURE 5B

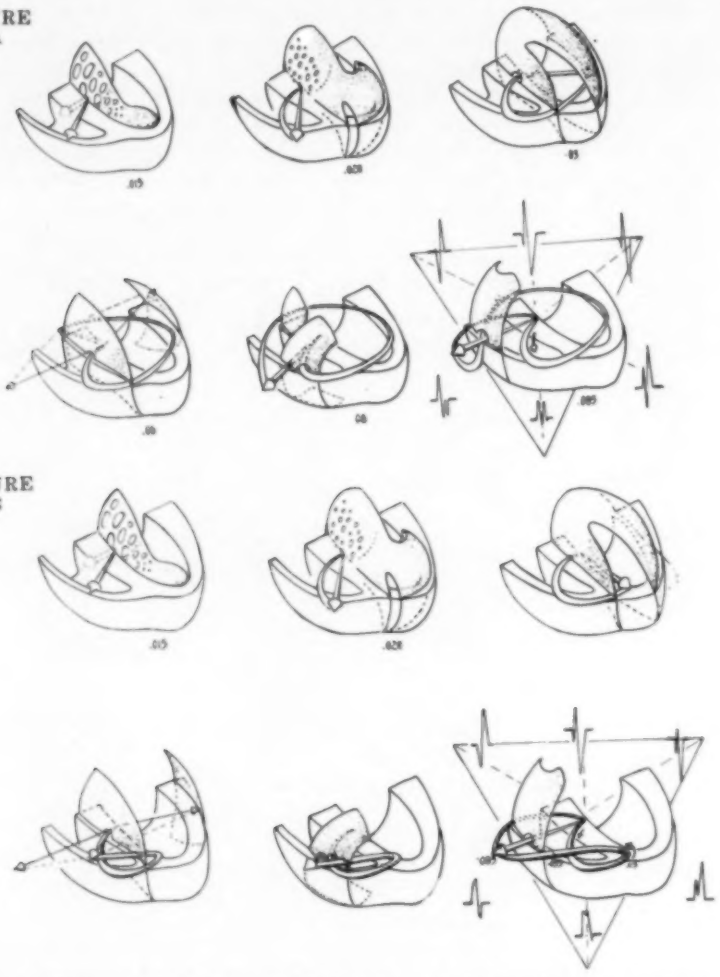

Figure 5: Diagram of the lower half of the ventricular portion of a semitransverse counterclockwise rotated heart showing the waves of excitation and spatial QRS loops produced in the presence of complete bundle branch block. The spatial QRS loop developed in A, corresponds to that which has been described as characteristic of right bundle branch block when the cube system is employed. The alternative form shown in B (developed assuming a slightly different shape for the left ventricle) shows a clockwise inscribed loop similar to that shown in Figure 6. Actually the difference between A and B may be due not only to difference in the shape of the ventricles but possibly also to variation in the cardiac/torso relationship, to the presence of left ventricular hypertrophy (A), or to difference in the method of recording. (Reproduced from Gardberg, Manuel: *Clinical Electrocardiography.* Paul B. Hoeber, Inc., New York, with the kind permission of the publisher.)

cardiogram and vectorcardiogram is obvious and the relation of these findings to the architecture of the heart is hardly questionable in view of the autopsy and reliable operative evidence obtained in significant numbers of cases of this disease. While the right ventricle may be thicker than the left in some of these cases it is apparent that even when it is not the electrocardiogram and the vectorcardiogram frequently have the characteristics shown in Figure 3. As in the newborn these records reflect an exaggeration of the right ventricular effects, and in the vast majority of cases the horizontal QRS loop of the cube is predictable from the conventional leads if Leads V_{4R} and V_{5R} are recorded in addition to the conventional precordial leads.

Electrocardiograms obtained in some cases of pulmonary stenosis have the form shown in Figure 4B. They are also common in atrial septal defects. These electrocardiograms are especially characterized by the presence of the rsR′ complex in the right precordial leads, a finding that raises the question of the presence of disturbance in conduction in the right bundle branch. Because such records are so common among individuals with congenital heart disease and also occur in its absence the electrocardiogram and vectorcardiogram in right ventricular hypertrophy and in right bundle branch block require detailed comparison.

Complete Right Bundle Branch Block and/or Right Ventricular Hypertrophy

The electrocardiographic and vectorcardiographic diagnosis of right ventricular hypertrophy promises to remain entangled in the problems involved in the recognition of right bundle branch block. Since autopsy material is of no value to the solution of this problem it is necessary, in order to understand this dilemma, to review the theoretic origin of the QRS loop in right bundle branch block which has now been confirmed by the findings of Scher.[3] In the presence of complete right bundle branch block excitation proceeds in the free wall of the left ventricle and the left side of the interventricular septum for some 0.06 second (in adults) before the right ventricle is activated regardless of whether the right ventricle is hypertrophied or not (Figure 5). After the first three or four hundredths of a second (in adults) the septum becomes the predominant structure in the production of the cardiac potentials, and the free wall of the right ventricle produces the final vectors of the loop and the final deflections in the leads. The two common variants of the right bundle branch block loop shown in Figure 5 may differ in significance only in that they represent slight differences in the shape of the left ventricle,[9] but, at least in some instances, the difference may be due to differences in the method employed in recording, differences in cardiac-torso relationship and possibly the presence or absence of left ventricular hypertrophy. The second (B) is similar to the horizontal cube loop that is regarded as characteristic of right ventricular hypertrophy in that it is inscribed in a clockwise manner. The distinguishing feature is that its terminal portion is inscribed much more slowly.

What has been said of the loops also applies to the complexes in the conventional leads. The complexes seen in right bundle branch block are similar to those seen in right ventricular hypertrophy except that in the former condition the time required for the inscription of the latter por-

tions of the complexes is much greater (compare the duration of S in Leads I and V_6 and of R′ in V_1 in Figure 4A with those in Figure 4B). Thus there is seldom much difficulty in distinguishing right bundle branch block from right ventricular hypertrophy when the QRS duration is as much as 0.12 second. However, given a record showing complete right bundle branch block there is no way to determine whether right ventricular hypertrophy is also present regardless of whether the loop has the Form A or B of Figure 5. Furthermore, experience shows that the height of R′ in V_1 and the magnitude of the final vectors of the QRS loop are not entirely reliable for this purpose. One may be suspicious of right ventricular hypertrophy if R′ is unusually large in the presence of right bundle branch block as noted by Barker[10] but we have seen no discernible hypertrophy of the right ventricle at autopsy when R′ was in excess of 10 mm. and, conversely, we have seen right ventricular hypertrophy when R′ is as small as 5 mm.

Incomplete Right Bundle Branch Block and/or Right Ventricular Hypertrophy

Theoretical syntheses of the QRS potentials in the normal and in the presence of right bundle branch delay are presented in Figure 1A and 1C respectively. It is noted that in the normal (Figure 1A) the long axis of the loop is about perpendicular to the long axis of the heart because the early depolarization of the thinner right ventricle leaves a large wave of excitation unopposed in the free wall of the left ventricle. Because it is activated from both sides almost simultaneously the septum produces a relatively small effect. When conduction is delayed in the right bundle branch, excitation of the right ventricle and of the right side of the septum are delayed (Figure 1C); the large waves of excitation in the left ventricle are now opposed by the excitation of the left side of the septum and by the delayed activation of the free wall of the right ventricle. As a result the vectors occurring at 0.04 to 0.06 second are shorter than those that occur at the same time in the presence of normal conduction and the loop becomes altered as shown in Figure 1C. In right ventricular hypertrophy of moderate degree the large waves of excitation that normally occur in the free wall of the left ventricle are opposed by waves of excitation in the right ventricle that are larger than normal and that persist longer than in the normal because of the increased thickness of that structure (Figure 1B). The septum is depolarized just as in the normal and no added septal effect is expected such as that which occurs in right bundle branch delay. The loop that results is similar to that which was developed for right bundle branch delay of 0.02 second.

The similarity between the theoretic loops of a lesser degree of right bundle branch delay (Figure 1C) and of moderate right ventricular hypertrophy (Figure 1B) is due to the fact that the greater rightward septal effects due to right bundle branch delay when added to the delayed right ventricular effects give opposition to the left ventricular effects that is similar to that offered by the larger than normal and more persistent waves of excitation occurring in the right ventricle when right ventricular hypertrophy is present.

The differences in the theoretic constructions of the complexes of Lead V_1 for right bundle branch delay and for right ventricular hypertrophy

disappear easily if the apex of the heart with right ventricular hypertrophy is pushed back for then a small R will be followed by a small S derived from the apices of the two ventricles and the R′ would follow at about 0.025 second (Figure 2). Thus this lead may be useless in distinguishing right ventricular hypertrophy from right bundle branch delay. The fact that the theoretic approach always develops a deeply notched R or S in Leads V_2 and/or V_3 in the presence of right bundle branch delay[9] is interesting in view of Gordon Myers'[11] suggestion that this finding is encountered in right bundle branch delay.

We have concluded (vide supra) that as a result of the proximity of the right ventricle to the anterior chest wall the conventional leads and the cube method of vectorcardiography exaggerate the electrical effects of right ventricular activation in the presence of right ventricular hypertrophy so that the horizontal loop when recorded is inscribed in a clockwise manner rather than as shown in the theoretic figure (Figure 1B) and the RS complex in V_1 shows a preponderance of R over S. Given the same relationship between the heart and the torso this same effect must be expected in the presence of right bundle branch delay for the septum is not much further from the anterior chest wall than is the free wall of the right ventricle, and because the net result of the combination of septal and delayed right ventricular effects that occurs when conduction is delayed in the right bundle branch is similar to that of the persistence of the right ventricular effects that occur in the presence of hypertrophy of the right ventricle. Thus the distortions inherent in the common methods of recording (including the Frank system) may be expected to result in the clockwise inscription of the loop of right bundle branch delay as well as of the loop of right ventricular hypertrophy. It is to be noted that with slightly greater degree of right bundle branch delay even the theoretic loop may be inscribed in a clockwise manner (Figure 1D). The shape of the left ventricle is another determining factor. Thus the recorded vectorcardiographic loop may be expected to be useless in distinguishing between right

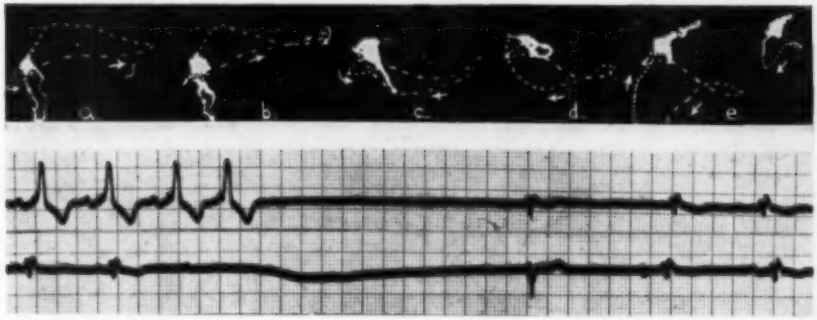

FIGURE 6: A continuous strip of Lead V_1 and horizontol loop of the cube vectorcardiogram from a subject with varying degrees of right bundle branch block produced by changing the heart rate with carotid sinus stimulation. Loop *a* shows (presumably) normal conduction and corresponds to the QRS complex shown in V_1 that follows the long pause; *e*, showing complete right bundle branch block corresponds to the first four QRS complexes shown in V_1; *b*, *c*, and *d*, representing intermediate degrees of right bundle branch block correspond to the rsR′ complexes shown in V_1.

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ventricular hypertrophy and right bundle branch delay. In the degrees of the latter condition under discussion the final portion of the loop will not be inscribed sufficiently slowly to permit the recognition of the conduction disturbance. More recently we have had the opportunity to confirm the accuracy of these inferences by direct observations[12] made on a patient with varying degrees of right bundle branch block (Figure 6).

When the cardiac/torso relationship is such that the exaggeration of the right ventricular effects is not marked, or if left ventricular hypertrophy increases the left ventricular effects, Lead V_1 may not have the characteristics shown in Figure 2 and the loops in right ventricular hypertrophy and in slight right bundle branch delay may be inscribed more nearly as drawn for the theoretic loops of Figures 1B and 1C. Under these circumstances both conditions might be unrecognizable. Evidence in support of this statement is found in the effect of respiratory variation of the cardiac/torso relationship upon the loop in the presence of right ventricular hypertrophy and in the normal infant. In some normal infants the horizontal loop recorded with the cube system varies during quiet respiration from clockwise to counterclockwise inscription.[8] We have noted a similar respiratory variation in patients with pathologic right ventricular hypertrophy. Thus the variability of the cardiac/torso relationship together with the frequent impossibility of distinguishing between the records of right bundle branch delay and right ventricular hypertrophy and the not infrequent occurrence of left ventricular hypertrophy probably account for much of the lack of correlation between the electrocardiographic and vectorcardiographic signs of right ventricular hypertrophy on the one hand and the autopsy findings on the other. Furthermore, given the proper cardiac/torso relationship the exaggeration of the right ventricular effects may reach such proportions that even in the absence of right ventricular hypertrophy or of right bundle branch delay V_1 and the horizontal loop of the cube may show the form seen in Figure 7. In other normal individuals, late excitation of the base of the interventricular septum, the crista supraventricularis, or the conus area of the right ventricle may be greatly exaggerated by the cardiac/torso relationship resulting in a prominent R′ in Lead V_1.

Finally it seems unavoidable to entertain the notion that right bundle branch delay frequently occurs under the conditions that account for right ventricular hypertrophy. In the experimental animal the slightest trauma to the right bundle branch produces block. During catheterization right bundle branch block may be produced by the pressure of the catheter against the septal wall. With increased rate right bundle branch block frequently develops even in absence of disease. It should not be surprising if increase in the intraventricular pressure or increased diastolic tension could be capable of producing the same effect. It is probable, therefore, that in some cases the appearance of the record is due in part to right ventricular hypertrophy and in part to right bundle branch delay.

The Electrocardiographic and Vectorcardiographic Diagnosis of Right Ventricular Hypertrophy

Electrocardiograms of individuals with right ventricular hypertrophy form a spectrum at one limit of which is the normal electrocardiogram, and at the other, records like those of Figure 3B. In addition a large

group of such records show characteristics that run the entire gamut of changes that may be seen in right bundle branch block (of all degrees). Records showing an exaggeration of the usual early infantile record (Figure 3) may be considered as evidence of right ventricular hypertrophy at any age. When the usual early infantile record persists later into infancy right ventricular hypertrophy may be suspected but no sharp limits can be assigned at this time for the age at which such records must be considered abnormal. It should also be pointed out that in some cases of posterior-lateral infarction and in some cases of emphysema high R waves may be seen over the anterior wall even in the absence of right ventricular hypertrophy. Criteria involving measurements of the deflections in Lead aVR alone are to be condemned, not only because they are erroneous when examined in our cases but because of the fundamental principle that no electrocardiographic interpretation should be based upon the characteristics of a single lead. When combined with the measurement of the mean manifest electrical axis, measurements in Lead aVR as a criterion of right ventricular hypertrophy are found wanting 1) in that they eliminate the diagnosis in some cases in which it can be established by the more conven-

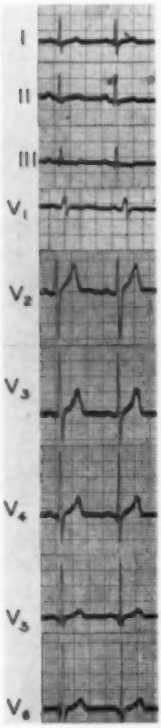

FIGURE 7A

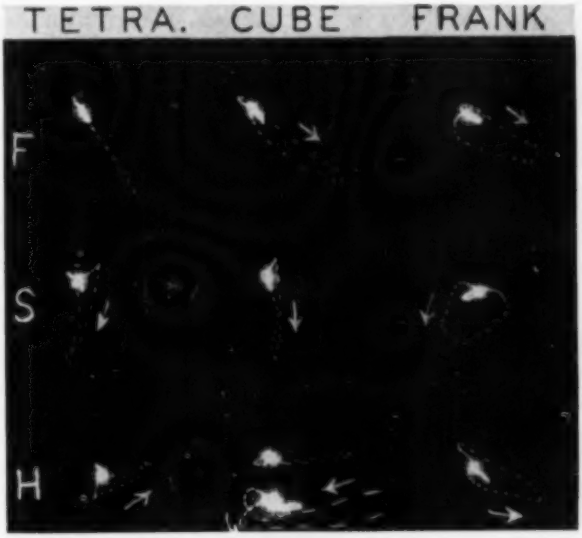

FIGURE 7B

Figure 7: Electrocardiogram (A) and Vectorcardiogram (B) of a normal subject showing a wide R wave in V_1 and inscription of the returning limb of the horizontal QRS loop (cube) anterior to the origin. Note that the Frank loop is also inscribed predominantly anteriorly. (The polarity of the Frank sagittal loop as we recorded it, is opposite that of the other two systems.)

tional criteria; 2) in that they suggest right ventricular hypertrophy in normal apex-back hearts with right axis deviation. Obviously Lead aVR is of no help in distinguishing right bundle branch block from right ventricular hypertrophy.

The T wave in Lead V_1 is usually inverted in the infant after the first few days of life and when the T wave is upright in Lead V_1 in infants over two months of age the presence of right ventricular hypertrophy must be strongly suspected.

There can be no question that the theoretical principle that the phase relations between two accurate leads (if such did indeed exist) as revealed in loops can reveal information regarding the direction and magnitude of electrical forces that cannot be readily discerned from these same leads examined independently. However, it is generally agreed that all leads made between any two points on the surface of the body are distorted by contour-eccentricity effects (even if we accept single dipole representation). It follows that the phase relationship between two such leads cannot be above suspicion insofar as accurate reflection of the direction and magnitude of the electrical forces is concerned. However, a method need not be accurate to be useful.

Given two even approximately accurate leads, or two leads in which the errors are systematic and correlative, it should be possible in some areas to gain some additional knowledge from the accurate portrayal of the phase relations in terms of loops. It may even be possible to turn the errors of such leads to advantage. Thus far, advantages that might accrue to the study of the cardiac potentials in terms of the vectorcardiogram have been obscured by a large accumulation of uncritical, hasty conclusions.

When the horizontal QRS loop of the cube *of nearly normal duration* is inscribed clockwise and markedly anteriorly in older children and adults it is indicative of right ventricular hypertrophy unless it is due to posterolateral infarction. In such cases the electrocardiogram, if Leads V_{3R} and V_{4R} are also recorded, are just as conclusive. However, the coexistence of a degree of right bundle branch block cannot be ruled out.

It must be emphasized that when the electrocardiogram and vectorcardiogram show characteristics that suggest right bundle branch block and/or right ventricular hypertrophy, proper interpretation rests to a considerable extent on correlation with the other data. In the presence of clinical and roentgenographic evidence collaborating a diagnosis of right ventricular hypertrophy such records are more significant than as isolated findings. For example, the patients whose tracings are shown in Figures 4A and 6 presented no clinical or roentgenographic evidence of heart disease and the diagnosis of right ventricular hypertrophy was not seriously considered. On the other hand, the typical murmur of pulmonic stenosis and roentgenographic evidence of right ventricular enlargement in the patient whose tracing is shown in Figure 4B suggests the opposite conclusion.

SUMMARY

1. The electrocardiogram and cube vectorcardiogram may fail to indicate the presence of right ventricular hypertrophy and may also fail to indicate the presence of small delays in conduction in the right bundle branch.

2. The electrocardiogram and cube vectorcardiogram are equally unsuitable for the distinction of right ventricular hypertrophy from incomplete right bundle branch

block (except in cases in which abrupt slowing by carotid sinus pressure reveals the presence of right bundle branch block).

3. Complete right bundle branch block may be readily recognizable in either the cube vectorcardiogram or the conventional leads but in such cases there is no reliable criterion for the detection of the presence or absence of coexisting right ventricular hypertrophy.

4. When the electrocardiogram and vectorcardiogram show characteristics that are typical of right bundle branch block and/or right ventricular hypertrophy proper interpretation depends upon correlation with other findings.

5. Reliable electrocardiographic criteria for the diagnosis of right ventricular hypertrophy cannot be presented in the form of a table of approximate limits for the various deflections, of the manifest electrical axis or simple combinations of these.

RESUMEN

1. El electrocardiograma y el cubo-vectorcardiograma pueden dejar de indicar la hipertrofia ventricular derecha y también la presencia de pequeños retardos en la conducción del haz de rama derecha.

2. El electrocardiograma y el cubo-vectorcardiograma son igualmente inadecuados para la distinción entre la hipertrofia ventricular derecha y el bloqueo incompleto de rama derecha (excepto en los casos en los que una lentitud repentina por la presión del seno carotideo revele la presencia de bloqueo de haz de la rama derecha).

3. El bloqueo completo del haz de rama derecha puede reconocerse facilmente ya sea en el cubo-vectorcardiograma o en las derivaciones habituales, pero en tales casos no hay un criterio de crédito para el descubrimiento de la presencia o ausencia de hipertrofia ventricular derecha coexistente.

4. Cuando el electrocardiograma y el cubo-vectorcardiograma muestran las características de bloqueo de haz de rama derecha y/o hipertrofia ventricular derecha, la interpretación adecuada depende de la correlación de otros hallazgos.

5. El criterio electrocardiográfica digno de crédito para el diagnóstico de hipertrofia ventricular derecha, no se puede presentar en la forma de un cuadro de límites aproximados para las varias deflexiones, para el eje eléctrico de manifiesto o para las simples combinaciones de éste.

RESUME

1. L'électrocardiogramme et le vectocardiogramme peuvent faillir à indiquer la présence d'hypertrophie ventriculaire droite, et également la présence de petits retards de la conduction dans le bloc de branches droit.

2. L'électrocardiogramme et le vectocardiogramme sont sans intérêt pour distinguer l'hypertrophie ventriculaire droite d'un bloc de branche droit incomplet (sauf dans les cas où une chute soudaine par la pression du sinus carotidien révèle la présence d'un bloc de branche droit).

3. Un bloc de branche droit complet peut être facilement reconnaissable soit dans le vectocardiogramme, soit dans les tracés conventionnels, mais dans de tels cas, il n'existe aucun critère valable pour détecter la présence ou l'absence d'hypertrophie ventriculaire droite coexistante.

4. Quand l'électrocardiogramme et le vectocardiogramme montrent des caractéristiques typiques du bloc de branche droit et/ou de l'hypertrophie ventriculaire droite, l'interprétation correcte dépend de la corrélation avec les autres constatations.

5. Des critères électrocardiographiques valables pour le diagnostic de l'hypertrophie ventriculaire droite ne peuvent être présentés sous forme de tableau des limites approximatives des différentes déviations, de l'axe électrique principal ou des simples combinaisons de ces éléments.

ZUSAMMENFASSUNGEN

1. Das Elektrokardiogramm und das Kuben-Vektorkardiogramm können versagen bei der Feststellung einer Hyperthrophie des rechten Ventrikels und können ebenfals versagen bei der Feststeilung geringer Verzögerungen in der Leitung im rechten Schenkel des Reizleitungssystems.

2. Das Elektrokardiogramm und das Kuben-Vektorkardiogramm sind gleichfalls ungeeignet zur Unterscheidung einer Hyperthrophie der rechten Kammer von einem inkampletten Block des rechten Schenkels des Reizleitungssystems (ausgenommen in Fällen, in denen eine abstrukte Verlangsamung durch Druck des Karottis-Sinus das Bestehen eines Blockes des rechten Schenkels des Reizleitungssystems ergibt).

3. Kompletter Block des rechten Schenkels des Reizleitungssystems lässt sich rechtzeitig erkennen, sowohl im kubischen Sektorkardiogramm als auch in den gewöhnlichen Ableitungen, aber in diesen Fällen ist es kein zuverlässiges Kriterium für die Feststellung des Bestehens oder nicht Vorhandenseins einer gleichzeitigen Hyperthrophie der rechten Kammer.

4. Zeigen Elektrokardiogramm und Vektorkardiogramm Merkmale, die typisch sind für einen Block des rechten Schenkels und/oder eine Hyperthrophie des rechten Ventrikels, so hängt die richtige Deutung von der Kortelation mit anderen Befunden ab.

5. Zuverlässige elektrokardiographische Kriterien für die Diagnose einer Hyperthrophie des rechten Ventrikels können nicht in Form einer Tabelle dargestellt werden mit annähernder Abgrenzung für die verschiedenen Ableitungen, die elektrische Hauptachse oder einfache Kombinationen von ihnen.

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Intracardiac Surgery Using the Kay-Anderson Heart Lung Machine*

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In 1951, Miller, Gibbon, and Gibbon,[1] described a stationary screen oxygenator. Following this, Kay and Gaertner[2] described a simplified stationary screen oxygenator. During the past year and a half, the stationary screen oxygenator has been further modified and simplified by Kay and Anderson.[3] The changes are as follows: First, the apparatus is made of stainless steel, pyrex and teflon so that the entire unit can now be autoclaved. A second important improvement is the single chamber construction. The single chamber for the collection of venous, coronary sinus and chest blood also acts as an oxygenating blood reservoir, filter chamber and air trap. This single chamber construction has eliminated much tubing, many connectors, and several containers. The amount of blood necessary for a procedure has been reduced, and the problems of cleaning, assembling and mechanical failure, have been lessened.

Venous blood from the superior and inferior vena cava enters one side of the chamber by gravity drainage. Oxygenated blood is pumped out of the other side of the container back to the patient's arterial system. An internal circuit pump sends the blood from the venous side to the distribution chamber at the top. The blood runs down the screens and is oxygenated as 97½ per cent oxygen and 2½ per cent carbon dioxide mixture flows by the screens. The internal circuit pump is run slightly faster than the arterial pump so that a greater flow leaves the venous side of the chamber than there is blood returning from the patient. This creates a small flow of blood from the oxygenated side to the venous side of the chamber and this prevents any venous blood from entering the arterial side.

In effect, there is a minimal left-to-right shunt in the bottom of the oxygenator. Blood aspirated from the heart and chest is returned by two large tubes to the venous side of the chamber. Blood in the bottom of the chamber acts as an air trap. A filter is incorporated on the oxygenating side.*

The third important variation is a filmer which was first described by Anderson, Anderson and Kay[4] in 1957.

This device paints a film on the screens. This obviates the necessity of first creating a saline film by filling the apparatus with saline and draining the saline as blood is added. The filmer consists of a sheet of teflon with a slot 1/16 of an inch wide for each screen to fit into. A handle at

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From the Cardiovascular Research Laboratory, Department of Surgery, University of Southern California School of Medicine and The Saint Vincent's Hospital, Aided by a grant from The American Heart Association.

*This Heart Lung Machine was kindly constructed for us by Corco, Inc., Los Angeles 34, California.

each end of the filmer allows the filmer to be raised to the top of the screens and then lowered. The filmer collects a pool of blood above it and as it is lowered, establishes the film on the screens.

The greatest benefit of this device is that blood is not circulated in the oxygenator except during by-pass. Prior to the use of the filmer, the film was established before any filling of the tubing and blood was circulated in the pump oxygenator 20 to 30 minutes before by-pass was started. This filmer has considerably shortened the length of time the blood circulates in the apparatus and thereby lessens destruction of the blood elements. Also, if the film for any reason becomes unsatisfactory, it can be re-established in a few seconds by pulling the automatic filmer to beneath the distribution chamber and then lowering it again.

The distribution chamber at the top of the oxygenator has also been modified. This has been done by making a solid floor for the bottom of the distribution block, and making small holes in the floor. We have found the slots between spacing bars and screen an unsatisfactory method of distributing the blood, since it is difficult to keep blood in the distribution chamber with this method.

Our clinical experience has consisted of operating upon 25 patients with this apparatus; three of whom had complete correction of their tetralogy of Fallot and are living and well. Two with atrial septal defects had complete closure and are completely well. Two had atrial septal defects and valvular pulmonic stenosis. These lesions were corrected and they are well. Eighteen patients had ventricular septal defects alone or associated with other defects. All 18 had complete correction of their defects.

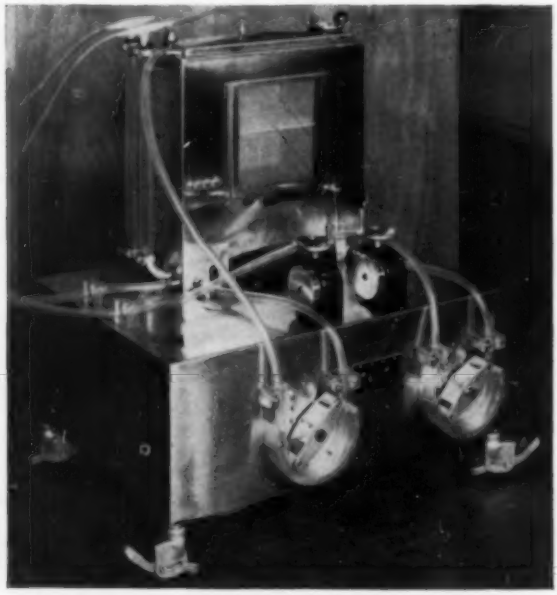

FIGURE 1: Photograph of Kay-Anderson heart lung machine which can be completely sterilized by autoclaving and consists of one chamber and two roller pumps.

Sixteen are living and well. One died 18 hours postoperatively of cardiac tamponade. Since then the pericardial sac has not been closed. The second patient who had pulmonary hypertension and was in congestive failure at the time of operation died three hours postoperatively.

Postoperative bleeding has been the same as one would expect with the routine thoracotomy. The bleeding has ranged between 75 cc and 250 cc's in the children, and at most 750 cc's in an adult. No patient has been returned to the operating room for bleeding. The chest catheters are removed 18 hours postoperatively. It has been unnecessary to do thoracentesis following removal of the catheters.

SUMMARY

A simplified stationary screen oxygenator capable of oxygenating and pumping 6 liters of blood per minute has been developed by the authors. This apparatus is sterilized by autoclaving. It has only one chamber. A film is established on the screens with an automatic filmer. The apparatus has been used clinically on 25 patients with 8 per cent mortality.

RESUMEN

Los autores han ideado un oxigenador simplificado, estacionario, de tipo de pantalla, capaz de oxigenar y bombear 6 litros por minuto.

Este aparato puede esterilizarse al autoclave. Tiene sólo una cámara. Se forma una película en la pantalla con un mecanismo automático.

Se ha usado este aparato en 25 enfermos en los que ha habido una mortalidad de 8 por ciento.

RESUME

Les auteurs ont établi un oxygénateur simplifié à écran fixe capable d'oxygéner et de pomper 6 litres de sang par minute. Cet appareil est stérilisé par autoclave. Il a un seul récipient. Un film est pris sur les écrans avec une caméra automatique. L'appareil a été utilisé cliniquement chez 25 malades avec 8% de mortalité.

ZUSAMMENFASSUNG

Es wurde von den Autoren ein vereinfachter stationärer Sieb-Oxygenator konstruiert, der imstande ist, 6 Liter Blut pro Autoklaven sterilisiert. Er hat nur eine Kammer. Die Siebe werden mit einer Membran versehen mit einem automatischen Filmer. In der Klinik wurde das Gerät angewandt bei 25 Kranken mit 8% Mortalität.

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Comments on the Early Diagnosis and Treatment of Patients with Congenital Heart Disease

Without overstating the case, it might be said that current management of patients with congenital heart disease is in a "state of flux." Much of this continual change is brought on by each new surgical development for the various specific lesions; but other factors contribute as well. As newer techniques are developed in diagnosis and in treatment, and as more experience is gained in the medical management of such patients, it is obvious to this author, that the general problem of congenital heart disease is becoming more and more one of dealing with younger and younger patients. It is this author's opinion that eventually the entire problem of diagnosis and of treatment will be best resolved *in the early infancy period of life*. The following are some of the reasons for this statement.

Of the babies born alive with congenital heart disease (approximately 1% of all live births[1]), nearly 75% die during the first two years of life, and most of these have lesions for which surgery is already well developed.[2] The majority of those infants that die and many that do not die, require periodic hospitalization for episodes of heart failure,[3] a manifestation in itself serious and frequently difficult to treat. With early diagnosis and treatment, many of these pangs of misfortune could be prevented.

Information already accumulated would indicate that certain patients with technically operable lesions, reach a stage of inoperability at an early age frequently in the absence of severe symptoms.[4, 5] If such patients are operated upon by current methods, death is almost a certainty. Other patients, with similar but less severe forms of the same disease, may survive surgery, but post-operative follow up to date has shown residual disease such as: persistent pulmonary hypertension and cardiomegaly.[6, 7]

More recently, the author has been made more acutely aware of the psychological advantages of early amelioration of cardiovascular signs and symptoms. A number of patients with congenital heart disease have been observed who have had complete surgical correction of the cardiac defect during adolescence. These patients, although cured of their physiologic and anatomic defect, have retained their psycho-social pattern of behavior of relative invalidism and of immaturity. In such patients, it would appear that the cardiovascular defect with its various implications had become an integral part of the personality of the patient. Thus the patient's "image of himself" has included a *defective heart* which has been difficult to repair short of extensive psycho-therapy.

Recommendations for the Future

In the Diagnosis: Physicians in charge of patients with congenital heart disease, must be made aware of the importance of early diagnosis. Early base line observations should be made on *all* patients suspected of having congenital heart disease; these observations should include roentgen examination of the heart and electrocardiography as well as a careful

history and physical examination with blood pressure determinations. Special diagnostic techniques should be developed and adapted for the small infant which would permit the determination of the position, direction and size of the cardiac shunts without removal of large amounts of blood. Better methods should be developed for determination of the anatomic status of the pulmonary vascular bed.

In the Treatment: Improvements should be made in the medical management of patients with congenital heart disease; this should include development of new drugs and better use of present drugs and diets. Present surgical techniques need to be altered to meet the requirements of the small infant under one year of age. Physicians and personnel need to have a better understanding of the psycho-dynamics of cardiovascular disease and its implications for the patient, family, doctor and community. Finally there needs to be a continual evaluation of present methods of therapy by follow up patients currently treated.

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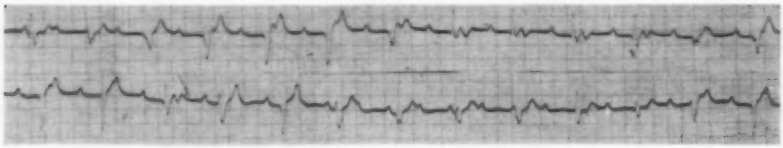
ELECTROCARDIOGRAM OF THE MONTH

Varying QRS Complexes in Complete A-V Block

These two strips (Lead I) were obtained from a 67 year old man with coronary sclerosis. No digitalis had been given. The second strip was recorded a few seconds after the first.

The atrial rate is approximately 136 and the ventricular rate is about 70. Since there is no relation between atrial and ventricular activity, complete A-V block is present.

The interesting feature of this electrocardiogram is the constantly varying form of the ventricular complexes. It is clear that some of these are combination beats arising from activation of the ventricles from two foci, discharging impulses almost simultaneously; thus certain areas of the ventricles are activated from one, while the rest of the ventricular muscle is activated from another center. At least three, perhaps four different foci, form impulses. The successive intervals between QRS complexes are, in hundredths of a second: 83, 82, 85, 84, 85, 88, 87, 84, 85, 85, 86, 83, 86, 87, 80, 88, 74, 84, 84, 79, 86, 85, 78, 86.



Varying forms of the ventricular complexes of the automatic beats are not rarely observed in complete A-V dissociation. They are especially apt to appear if bilateral bundle branch block is responsible for the complete A-V block. Automatic ectopic centers in different parts of the ventricles have usually the same rate of impulse formation. Therefore, when one center is delayed even for 1 to 2 hundredths of a second another promptly discharges in its place.

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X-RAY FILM OF THE MONTH

A hospital employee, colored man aged 47. Past history irrelevant. In good physical condition and asymptomatic. During periodic survey examinations a slowly progressing infiltrating lesion in the right upper lobe was discovered. Extensive, persistent and repeated clinical workups were all negative. On March 25, 1958, a sputum culture yielded a yeast like fungus, which was identified as Saccharomyces.

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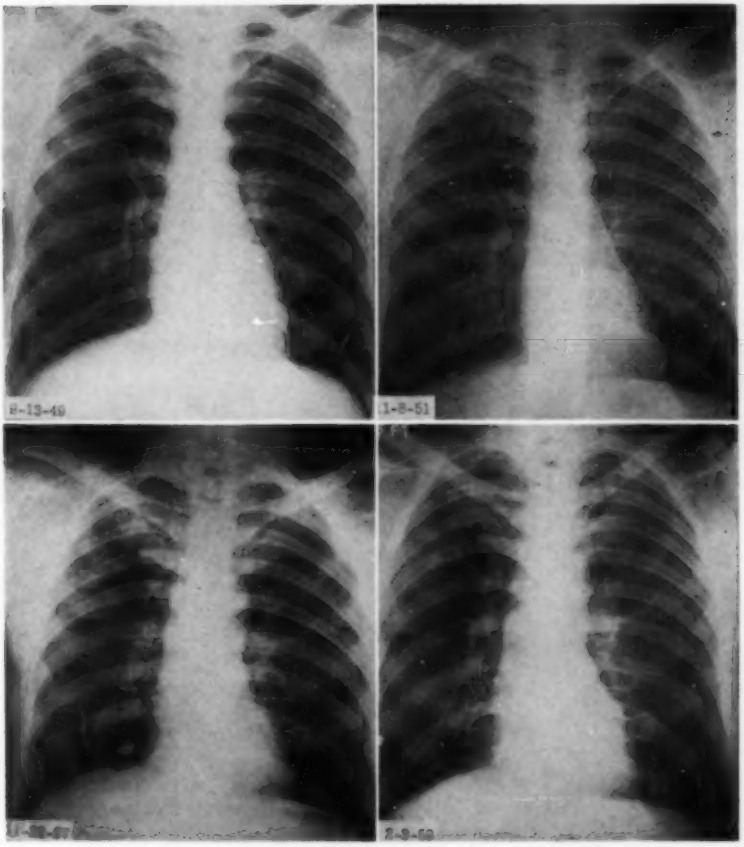

Case Report Section

Congenital Adenomatoid Malformation of the Lung

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In recent years the diagnosis of congenital cystic disease of the lung has been clarified and restricted as a result of the recognition of a variety of emphysematous and cystic lesions of diverse etiologies. True cystic disease is rare.[1] Rarer still is the closely related condition first reported in 1897 by Stoerk as "cystic fetal bronchial adenoma,"[2] and introduced in the English language medical literature in 1949 by Ch'In and Tang of Peking as "congenital adenomatoid malformation."[3] That the adenomatoid malformation is a variant of congenital cystic disease was acknowledged by Ch'In and Tang, but it is sufficiently distinctive to warrant recognition. Examination of published photographs indicates that the lesion in different cases varies from mainly solid, enlarged, tumor-like lobes to multicystic lesions. Moreover, as Craig, et al.,[4] point out, there are cases of true congenital cystic disease in which areas resembling the adenomatoid malformation are found upon pathological examination. It would appear possible to assemble a series of transitional cases linking true congenital cystic disease and the adenomatoid malformation. The following case is typical of the adenomatoid malformation and represents, we believe, the 28th reported case. Previously reported cases have been tabulated by Gottschalk and Abramson.[5]

Case Report

Case: The mother, aged 23 years, para I, gravida II, first visited her doctor in the sixth month of pregnancy. Examination revealed no abnormal findings. Her first child, aged 13 months, was reported to be alive and well. The mother returned to the office six weeks later with an extremely distended abdomen, the uterus being tense and tender. The blood pressure was normal. The fetal heart could not be heard. A

From the Department of Pathology, University of Alberta.

FIGURE 1: Cut surface of adenomatoid malformation. Fixed tissue.

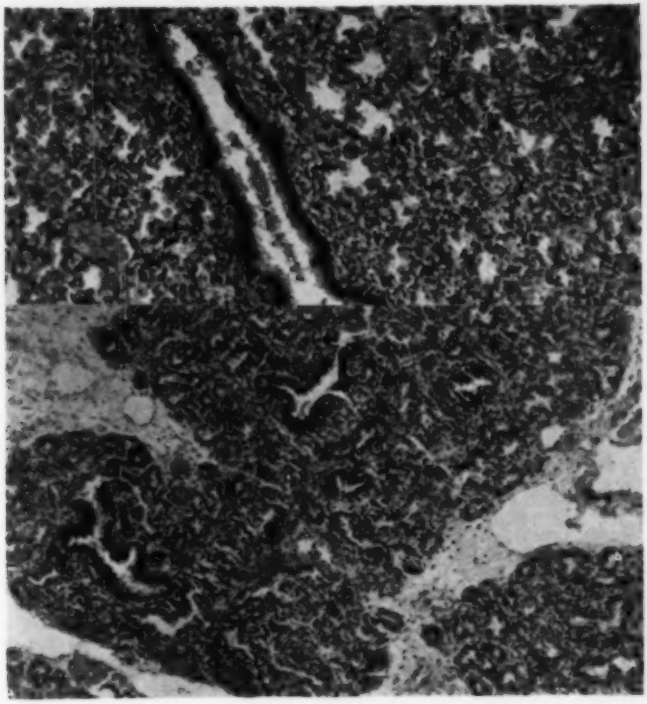

FIGURE 2: Normally developed, unexpanded left lung above, and fetal right lower lobe below.

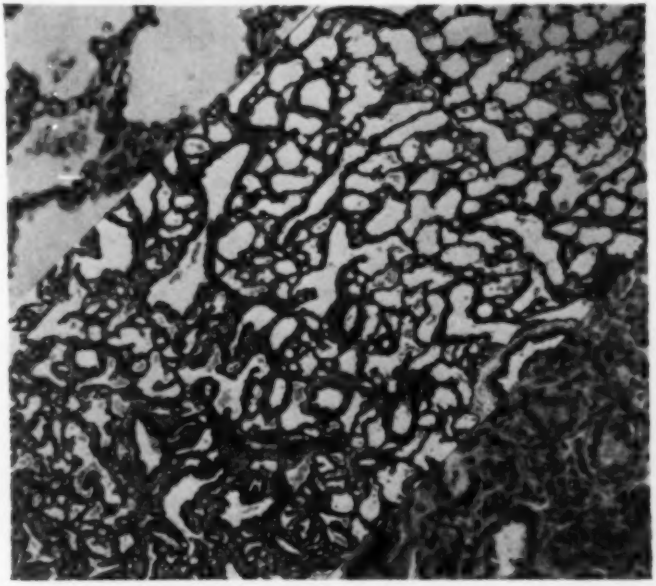

FIGURE 3: Peripheral portion of adenomatoid lobe with alveolar differentiation at top right and adenomatoid tissue at bottom left. Insets show under higher magnification alveolar development at top left and adenomatoid tissue at bottom right.

roentgenogram revealed a single vertex presentation. She was admitted to the hospital and the membranes were ruptured. Over 8 liters of amniotic fluid was released, and a stillborn girl was soon delivered. The placenta was normal.

Autopsy: (Relevant findings only). External examination revealed a 1,530 gram premature infant with crown-rump measurement of 25 cm. The chest appeared somewhat increased in anteroposterior diameter. The 10 gram left lung was grey-purple and atelectatic. Mediastinal structures were displaced toward the left by the massive, tumor-like, 100 gram right lung. Closer inspection revealed that the large, smooth, rounded, pink-grey mass represented the upper lobe of the right lung, the lower lobe consisting of a small, inconspicuous, grey-purple structure. No middle lobe was identified. The cut surface of the massive right upper lobe was solid, homogeneous, grey and fleshy with a few groups of irregular and deformed bronchial channels (Figure 1).

Histological Examination: The liver was the site of pronounced hemopoietic activity, in keeping with prematurity. The left lung was normal in structure and unexpanded (primary atelectasis). The small right lower lobe consisted of lobulated, fetal lung, but aside from retardation in development, was not malformed (Figure 2). The massive right upper lobe presented a striking adenomatous appearance characterized by great proliferation of bronchiolar structures without alveolar differentiation except in a narrow subpleural zone (Figure 3). In none of the many sections examined did bronchial structures have cartilage or tubular mucous glands in their walls. Many of them, however, were supported by narrow bands of smooth muscle. Some of the larger bronchi were irregular and tortuous with papillary infolding of their walls. An interesting finding was small groups of bronchioles lined by tall columnar epithelium with clear cytoplasm giving a strongly positive PAS reaction for epithelial mucin (Figure 4). Finally, it was noted that capillary blood vessels were inconspicuous in the supporting mesenchyme of the non-alveolated tissue, but comparatively abundant in the narrow subpleural zone in which alveoli were present.

DISCUSSION

The adenomatoid lobe bears little resemblance grossly to the usual form of congenital cystic disease. Five main features characterize the adenomatoid malformation and

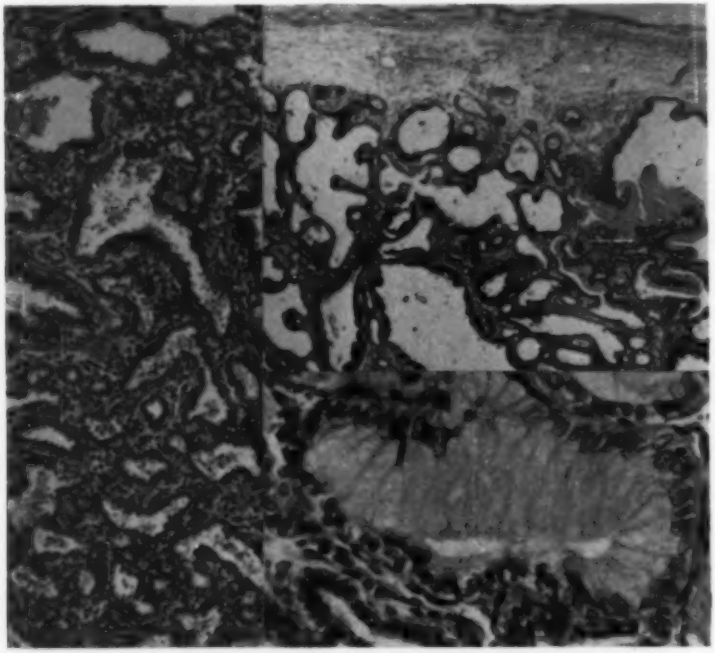

FIGURE 4: Structure of central portion of adenomatoid lobe is shown at the left. At top right are dilated subpleural malformed bronchi and a focus of columnar mucinous epithelium. Lower right shows mucinous epithelium under high magnification.

differentiate it from cystic disease: (1) absence of bronchial cartilage (2) absence of bronchial tubular glands (3) presence of foci of tall columnar mucinous epithelium (4) marked overproduction of terminal bronchiolar structures without alveolar differentiation except subpleurally (5) massive enlargement of the affected lobe. Areas of adenomatoid structure may be present in true cystic disease, but in the latter the cystic bronchi usually have cartilage or tubular glands in their walls.

Superficially, the adenomatoid malformation resembles fetal lung, except that it is not lobulated. The presence of alveoli at the periphery of the lobe is a puzzling, yet characteristic, finding. Craig et al.,[4] by increasing the intrabronchial pressure at operation, were able to demonstrate the inflatability of the malformed lobe in one case. The published photomicrographs from their four viable cases treated surgically show much more alveolar structure than did the case described in this report. In the present case alveoli were absent in some parts of the periphery of the malformed lobe; here the bronchial structures were dilated (Figure 4).

Characteristic of the adenomatoid malformation is the massive size of the affected lobe, which displaces other thoracic structures. This evidence of excessive growth led to the suggestion that the lesion may be a form of hamartoma,[6] although it has little in common with the cartilaginous lesion usually designated by that term. In true cystic disease the affected lobe may occasionally be enlarged, but here it is a result of hyperdistention due to a check-valve mechanism.[7]

The reported cases have been mostly premature stillborn infants, but a few have been born alive at term. In a few instances the abnormal lobe has been resected surgically, with survival and cure. The untoward effects of the disorder result from intrathoracic pressure effects with circulatory and respiratory embarrassment. Anasarca, a feature of 13 of the 27 reported cases, is attributable to such pressure effects. Polyhydramnios, a feature of four previous cases, was in each instance associated with anasarca. Polyhydramnios was present in our case, but not anasarca. Obstruction of venous return from the placenta has been considered the cause of the polyhydramnios.[5]

Addendum: Since this paper was submitted for publication, an additional case report has been published: Goodyear, J. E. and Shillitoe, A. J.: "Adenomatoid Hamartoma of the Lung in a Newborn Infant," *J. Clin. Path.*, 12:172, 1959.

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Acute Lipoid Pneumonitis Due to Aspiration of Pressurized Paint Droplets

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Lipoid pneumonitis is a well recognized disease entity with characteristic clinical and pathologic findings. Its etiology and pathogenesis, particularly with reference to the aspiration of certain lipid emollients, has been proved and documented.[2, 7] The disease was first observed in man by Laughlin,[4] who, in 1925, called attention to this distinctive pneumonic process which he attributed to the aspiration of liquid petrolatum hydrocarbons. The pulmonary lesions in these cases were similar to those he produced by the intratracheal injection of oily substances into the lungs of rabbits. The disease process produced by inhalation of reactive aerosol oil mists or of nebulized industrial oil dispersed by pressure sprays can be included in the same category with the lipoid pneumonitis produced by petrolatum aspiration.

A case of lipoid pneumonia with abscess formation resulting from the aspiration of a highly reactive drying oil contained in a commercial enamel paint is discussed in this report. The short duration of symptoms, the fulminating clinical course, and the histochemical findings in this case established the presence of another form of lipoid pneumonitis.

Case Report

J. T., Case No. 18688, a married man, 55 years of age was admitted to the Third (New York University) Surgical Service, Goldwater Memorial Hospital with chief complaints of fever, night sweats, and productive cough of three weeks' duration. During the period preceding admission he was treated in an out-patient clinic for an upper respiratory infection, but hospitalization became necessary because of persistent high fever and a rapid weight loss of 14 pounds. His past history was essentially noncontributory with the exception of syphillis contracted 14 years prior to admission for which he was treated by bismuth injections. Family history was non-contributory. The patient stated that he had been employed in the garment industry until six months prior to admission. At that time, during a period of unemployment, he sprayed a number of cabinets and refrigerators. This work was done with an electric paint sprayer in a small unventilated room without protective respiratory device. He completed the entire project within a period of about 30 days and noted no immediate ill-effects.

Admission physical examination revealed a well-nourished, but obviously ill man. Admission temperature was 101°F. Positive physical findings were limited to the chest. The percussion note was dull over the region of the left upper lobe of the lung anteriorly. The breath sounds were increased and coarse moist rales were audible over this same area. A posterioanterior roentgenogram of the chest and apicograms were interpreted as showing an area of infiltration in the apical and subapical region of the left upper lobe with a large abscess with a fluid level (Fig. 1). X-ray films of the skeleton showed no malignant bony involvement. The hemoglobin was 14 gms., the red blood count 3.5 million. The white blood cell count was 16,100 with a normal Schilling index. The erythrocyte sedimentation rate was 11 mm. corrected. The blood chemical determinations including blood urea nitrogen and fasting blood sugar were within the normal range. Smear, culture, and guinea pig inoculation of the sputum and gastric washings were consistently negative for the presence of tubercle bacilli. Papanicolaou studies of the sputum and gastric washings were negative for malignant cells. A blood Wassermann was negative.

Operative findings: Surgical exploration of the left lung was carried out by a posterolateral incision through the bed of the resected fifth rib. The apical portion of the left upper lobe was found to be adherent to the parietal pleura by thin fibrous adhesions. The mid-portion of the left upper lobe contained a hard firm mass about

From the Department of Surgery, College of Medicine, New York University, Bellevue Medical Center.

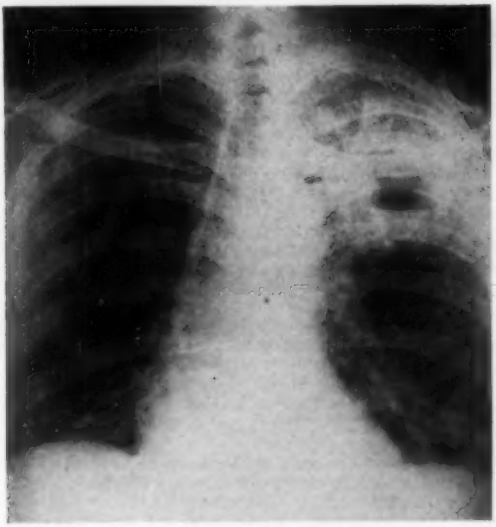

FIGURE 1: Posterioanterior roentgenogram of the chest showing an abscess cavity with a fluid level located in the subapical segment of the left upper lobe.

FIGURE 2

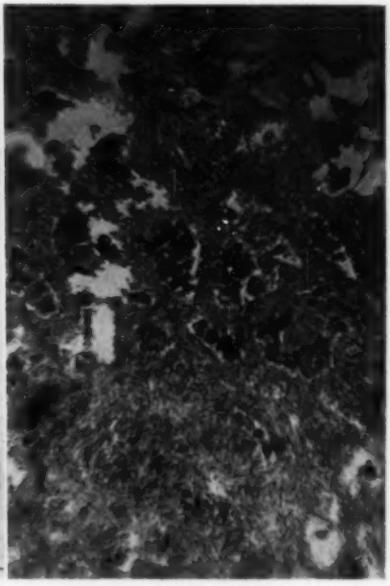

FIGURE 3

Figure 2: Photograph of the resected left upper lobe and lingula segment. The lung has been transected through the level of the abscess cavity.—*Figure 3:* Photomicrograph of a paraffin section taken from the subapical portion of the left upper lobe. Osmic acid stain; × 100. Note the irregular outline of the dark staining oily masses.

5 cm. in diameter. The lingular portion of lung appeared to be diffusely indurated. Left upper lobectomy and lingulectomy were performed.

Pathological studies of the left upper lobe and lingula segment showed the apical pleura to be fibrotic and partially consolidated. Contained within the substance of the lung was a necrotic area approximately 2 cm. in diameter, filled with thick purulent material (Fig. 2). There was the suggestions of a limiting wall in some areas of this abscess. A few small white pin-point nodules were seen in the tissues immediately around the area of necrosis. Microscopic examination disclosed a marked inflammatory reaction in the central portion of the lung. The alveolar septa were markedly thickened and contained inflammatory cells. The alveoli contained chronic inflammatory cells as well as a large number of lipoid bearing macrophages which stained orange-red with Sudan IV and black with osmic acid (Fig. 3). The abscess cavity was surrounded by large groups of mononuclear cells and many foam cells. Plasma cells predominated, the number of polymorphonuclear cells was relatively small. The bronchus adjacent to this area was marked by peribronchial chronic inflammation. The mucosal portions appeared to be less involved. Both the arteries and veins showed maximal sclerosis. The pleura on the surface of the section was fibrotic. There was no evidence of tubercle formation or neoplasia. Microscopic diagnosis was lipoid pneumonitis, chronic pneumonitis, abscess of lung. Special chemical studies were then performed in an effort to determine the characteristics of the lipids. A sample of the surgical specimen in the vicinity of the abscess was found to contain a total of 0.626 gms. of fat. The fatty acid content was 0.328 gms. The unsaponified fraction was 0.297 gms. (total weight of the dried sample was 7.0 gms.).

Comment: The patient made an uneventful recovery from the operative procedure. Follow-up roentgenogram (Fig. 4), one year later, showed good expansion of the left lower lobe. In view of the interesting and unusual pathological data he was reinterrogated to determine the duration of exposure to the inhalation of the enamel paint droplets. It was verified that the duration of the exposure did not exceed six weeks, and that the initial symptoms appeared within four weeks. He stated that he used an electric paint sprayer of the type employed by hobbyists, and never used a protective breathing device. He noted, also, the recurrence of a severe headache which lasted for several hours following each session with the pressure sprayer.

Discussion

In the present case report lipoid pneumonitis with abscess formation developed rapidly after a short period of exposure to the inhalation of an aerosol mist. Thus, it differed from the typical case descriptions in the literature, all of which emphasize chronic exposure to emollient hydrocarbons such as liquid petrolatum. The cicatricial nodular lesion of the lung induced by liquid petrolatum is particularly troublesome. This neoplasm mimics pulmonary malignancy clinically, roentgenologically and grossly at the

FIGURE 4: Posterioanterior roentgenogram showing the appearance of the chest one year after left upper lobectomy and lingulectomy.

operating table. Thomas and Rienhoff[6] and Brown and Biskind[1] have each reported single cases in which resections were performed for chronic lipoid pneumonitis, and Janes[3] reported two such similar cases in which lipoid pneumonia simulated a tumor necessitating pulmonary resection. At operation, the gross appearance of the tumorified area may often be so confusing that frozen section biopsy may be required.

The disease pattern as described here can be readily correlated with the experimental changes induced in the lungs of white mice exposed to various oil aerosol mists. In the experimental studies of Shoshkes,[5] it was proved that surfaces that oppose the airflow, namely the terminal bronchioles and alveolar ducts received the greatest impaction of oil particles. After such exposure oil droplets which were retained in the lung were removed by phagocytes and mocrophages with the ultimate development of a foreign body reaction of varying severity and resulting in focal areas of lipoid pneumonitis.

While it is generally claimed that oil aspiration pneumonia can be categorized by characteristic pathological lesions, it is far more reasonable to assume that the type pathology is dictated by the chemistry of the aspirated oil, and as such the clinical course of the disease is determined. According to Pinkerton[8] the reaction of the lung to the aspirated oil varies directly with the free fatty acid content of the aspirated oil.

From other experimental studies we have noted that the more unsaturated the oil, the easier the lung lipases can hydrolyze it to free fatty acids. The characteristic focal granulomatous lesion seen in the pulmonary parenchyma in the chronic form of the disease is a reaction to the aspiration of a chemically inert member of the paraffin group of hydrocarbons such as mineral oil.

It seems that the type pathology seen in this case, pneumonitis and lung abscess, was secondary to the aspiration of the highly reactive drying oil since both conditions were found in close proximity in the subapical portion of the left upper lobe.

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Germinoma of the Mediastinum: A Case Report with Special Reference to the Histogenesis of Mediastinal Teratoma

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There is no other space in the body like the mediastinum which harbor so many kinds of interesting tumors. We consider it worthwhile to report the following case because of its rarity and for a better understanding of this kind of tumor whose etiology is as yet not fully recognized.

Case Report

A 23-year-old man was referred to the surgical clinic because of an intrathoracic mass. He developed easy fatigability four months prior to admission and was treated outside for ankylostomiasis, and from which treatment he received no amelioration of his complaints. Just before admission to the surgical clinic, he was found to have an abnormal shadow on chest roentgenogram. There was no symptom referrable to an intrathoracic mass.

Physical examination revealed a well developed apparently healthy man. On percussion, there was noted an area of dulness extending from the second to the fourth intercostal space along the right sternal border. There was no other abnormal finding in the chest that could be noted.

Laboratory data indicated the following: Urinalysis was negative; Hemoglobin, 12.2 Gm.; RBC, 3,750,000; WBC, 6,300; Schilling differential was within normal limits.

An x-ray film of the chest showed a mass in the anterior mediastinum (Fig. 1). Fluoroscopic examination revealed no pulsation of this mass with well functioning diaphragm on both sides.

Thoracotomy was done through an anterior approach under local anesthesia after preparatory right artificial pneumothorax for one week. After resection of the car-

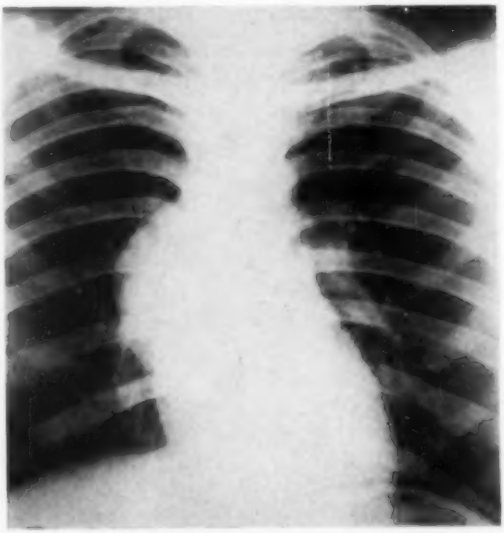

FIGURE 1: Posteroanterior roentgenogram of the chest.

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tilages of the second, third and fourth ribs, a well encapsulated mass was exposed. It extended into both thoracic cavities and was loosely attached to the surrounding tissues. The mass was removed extrapleurally without difficulty.

Gross findings of the specimen: The mass, measuring 9.0 x 8.5 x 4.0 cm., weighing 159 Gm., was well encapsulated. On section, it was grayish-white, soft in consistency and parenchymatous in texture. There was a dark area of necrosis with liquefaction in the central part.

Microscopic section revealed a typical seminomatous tissue with well defined groups of large cells having clear cytoplasm set in a connective tissue framework accompanied by a variable number of lymphoid cells (Fig. 2). In the different cut sections, more atypical features in the nuclei and its chromatin content were noted and mitotic figures were encountered more frequently. Residual thymic tissue was found in the marginal areas of the tumor (Fig. 3). However, no teratomatous elements were seen despite extensive histological examination.

The postoperative course was uneventful and he is well four years after the operation. Recent examinations revealed no abnormality in his chest or testes.

DISCUSSION

There are few reports dealing with seminoma or seminomatous tumors developing in the mediastinum. Friedman[1] was possibly the first to describe seminomatous tissue in the mediastinum. He studied the anatomical pathology of 30 mediastinal teratomas comparing with testicular neoplasm by the multiple block method and found a germinoma pattern in three of them. He ascribed extragonadal germ cells to be the

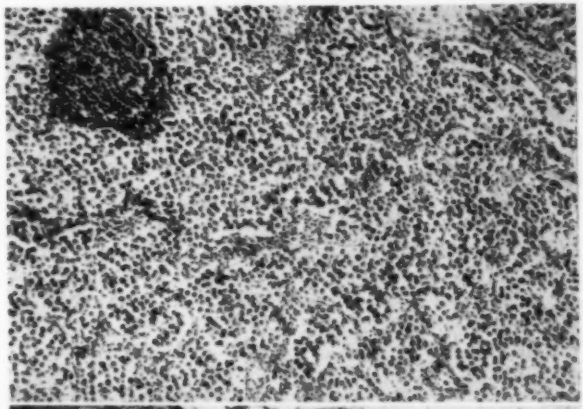

FIGURE 2

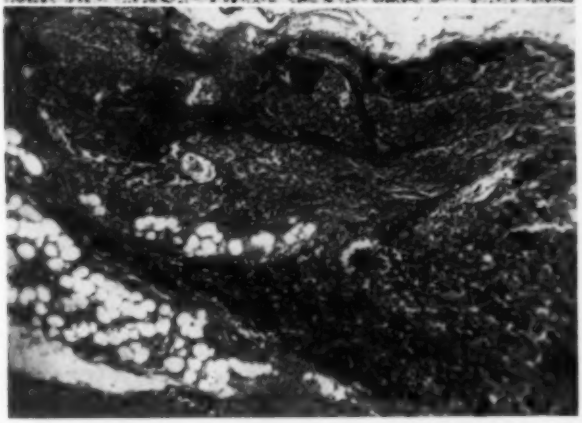

FIGURE 3

Figure 2: A microscopic section showing typical seminomatous tissue in alveolar arrangement. Hematoxylin-eosin stain (x150).—*Figure 3:* Microscopic section showing residual thymic tissue in marginal area of the tumor. Arrow indicates Hassall's corpuscle. Hematoxylin-eosin stain (x50).

origin of mediastinal teratomas and gave the following schema of development of teratomas (Fig. 4). The term germinoma was preferred by him for cases of dysgerminoma of the ovary, seminoma of the testis and for identical tumors which occur extragenitally.

Pugsley and Carleton[2] reported a case of mediastinal teratoma in which germinomatous areas and residual thymic tissues were found and a case of chorioepithelioma of the thymus. In both of them neither neoplastic tissue nor scar was found on serial section of the testes. He supported Friedman's view.

Woolner et al[3] reported three cases of seminoma (germinoma), apparently primary, in the anterior mediastinum, two of which were pure seminoma, and the other a case of malignant teratoma which contained foci of seminoma on multiple block section. The first case was a 31-year-old man with multiple metastases and who was benefited by irradiation after surgical extirpation of the mediastinal mass. He was reported to be well three years after the operation with no abnormality in the testes during that period. The second case was a 24-year-old man with a mediastinal mass found to be unresectable at thoracotomy and which completely disappeared after 13 daily x-ray exposures. The third case was a 23-year-old man, who died with signs of spinal cord compressions, two and one half months after extirpation of the mediastinal mass. Based on their clinical observations, they claim that these tumors were apparently primary in the mediastinum, although no histologic examination of the testes was made in any of their cases.

Recently, Iverson,[4] attempting to reclassify thymic tumors, reexamined 50 specimens previously diagnosed as thymomas at the Armed Forces Institute of Pathology during two years from 1952 to 1954. He recognized that eight cases previously diagnosed as thymic carcinoma were all seminomatous tumors and in addition, a definite relationship to teratoid tumors was noted in three of the cases. As to the site of origin, he suggested the possibility of either the thymus or the mediastinum, though the tissue of origin was considered to be the same in either case.

Effler and McCormack[5] stated that they have experienced two anterior mediastinal seminomas among 27 thymic neoplasms. However, they did not give details and McCormack[6] himself did not believe that these tumors were derived from the thymus per se.

In the reported case, residual thymic tissues were found in the marginal areas of the tumor and hence intrathymic development is highly probable.

However, Friedman's concept was challenged by Willis[7] and Mostofi.[8] Schlumberger,[9] having found thymic tissue in four out of 16 anterior mediastinal teratomas, pointed out the close relationship between the thymus gland and mediastinal teratoma. He concluded that teratoma of the anterior mediastinum has its origin in the faulty embryogenesis of the thymus, although he concedes that teratoma of the testes or the ovaries arise from germ cells. Castleman[10] briefly mentioned these tumors in his monograph and considered them to be a form of teratoma because of the presence of teratoid elements which were usually noticeable. In the case reported, no teratoid

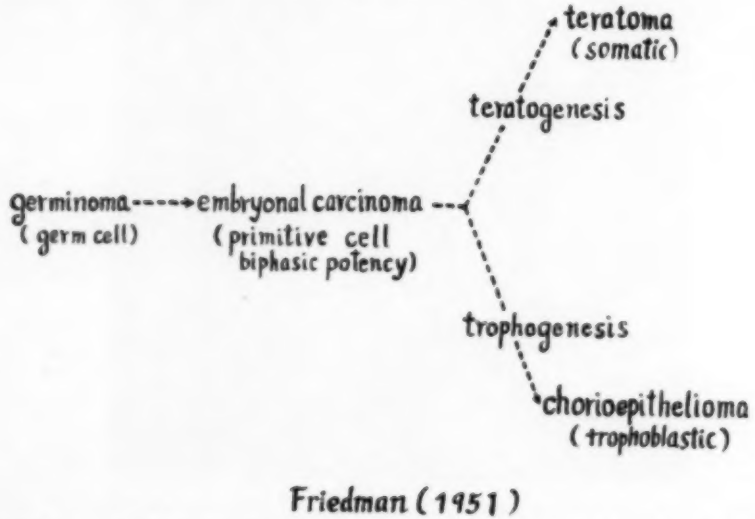

FIGURE 4: Diagram postulating interrelationship of tumors of germ cell origin (Friedman 1951).

element was found in the whole tumor tissue by the multiple block method. It is hardly conceivable that the seminomatous tissue represents an overgrowth of a teratoma with destruction of the remaining elements. Since, by Friedman's concept, the germinoma precedes the teratoma, it is not surprising that no teratoid element was found in our case.

It goes without saying that before these tumors are accepted as primary, one should rule out by careful pathologic examinations the presence of a primary tumor in the testis or ovary. In the case reported, it is probably justifiable to consider it primary because neither metastases anywhere nor abnormal findings in the testis was noted four years after surgical extirpation. These cases indicate that primordial germ cells might be misplaced in the mediastinum, probably in the thymus per se, and occasionally may give rise to these tumors. However, further embryological studies are needed.

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Treatment of Pulmonary Aspergillosis

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Treatment of most of the pulmonary mycoses has been unsatisfactory until the advent of a new antifungicidal drug, Amphotericin B. This has so far shown promise of being a useful addition to the meager stock of therapeutic weapons we now have available.

Aspergillosis, and particularly pulmonary aspergillosis, has not been much of a problem in the past because of its rarity. This, however, is not much help to the one patient who happens to be unfortunate enough to develop it. The increase of fungal infections seems to be general throughout this country in the past few years and may make this more or less unknown disease more frequent and increase the need for an effective remedy.

Since the lack of clinical cases, which makes this a special problem, also acts to hinder research, it is important to report results—good or bad—from any new method of treatment. This follows even though there may be no statistical value to the report.

Amphotericin B has been and is being used in the treatment of fungal infections of many types. In some cases it has proved of more value than in others. So far there is no report on its use in the treatment of aspergillosis. It has now been used successfully in one case of pulmonary aspergillosis, which is the basis of this report.

Mrs. S. Z., a 61 year old, white woman of Russian descent, gave a past history of pulmonary tuberculosis since 1937. This was treated with right-sided pneumothorax, and she was clinically well until July of 1954. Then she developed recurrence of the disease on the right side with positive sputum. She was admitted to a sanatorium and treated with streptomycin and sodium para-aminosalicylate for almost two months, at which time streptomycin was discontinued and isoniazid was substituted. The antibiotics converted her sputum and her condition improved clinically so she left the sanatorium and returned home still on antituberculous drugs.

In May of 1956, she was about to discontinue the drugs when she fell and broke a hip. This was pinned and because of the trauma from the surgery and the fracture, it was decided safer to continue chemotherapy. This was therefore continued until December 1956 when she was discharged with the diagnosis of pulmonary tuberculosis, far advanced, inactive.

Some months later she developed a cough with slight loss of weight. The cough did not respond to non-tuberculous antibiotic therapy, nor did it respond to a retrial of antituberculous drugs, including seromycin.

X-ray films and sputum examinations were negative for any change during this time.

On May 28, 1957, fluoroscopy showed the presence of air and fluid in the right pleural space, confirmed by x-ray film. She was admitted to the hospital and the fluid was aspirated. This revealed a pure culture of Aspergillus fumigatus. The diagnosis of the particular species of fungus was made at the Communicable Disease Center of the Public Health Service at Chamblee, Georgia.

Injection of dye into the pleural space at the time of aspiration and subsequent expectoration of the dye revealed the presence of a broncho-pleural fistula as had been suspected. Penicillin and streptomycin were injected into the pleural space with no particular benefit, and she ran a rather high fever during this period. When the diagnosis was confirmed, and due to the absence of other methods of treatment, and in spite of the possibility of reactivating her tuberculosis, she was started on potassium iodide, 5 grains 3 times per day. This was increased until it reached the dose of 50 grains 3 times per day. She seemed to get some benefit from this massive iodide therapy but still had fever and was quite sick.

In the beginning of July a supply of Amphotericin B was obtained through the courtesy of Doctor Hildick-Smith, Associate Medical Director of the Squibb Institute for Medical Research. Nothing was known about the dosage of this drug in the treatment of Aspergillosis, but from experience and treatment of other mycoses, we started with a dose of 10 mg. dissolved in 500cc of 5 per cent glucose and given intravenously over a period of not less than six hours. This was given daily and slowly increased, with the

exception of one day of rest. This was ordered because of a slight increase in the nitrogenous constituents of the blood and the feeling that the drug might be doing some damage to the kidneys. However, the one day of rest was sufficient to return the blood picture to normal and the medication was continued, finally reaching a dosage of 35 mg. per day by the 21st of July. On three occasions 5 mg. of a concentrated solution of the drug were injected intra-pleurally.

Her temperature, which had been running between 101 and 102°F, came down to normal a short time after the use of the Amphotericin B. Her cough markedly diminished and injection of dye intra-pleurally did not lead to presence of the dye in the sputum and therefore it was apparent that the broncho-pleural fistula had closed. She had received a total of 390 mg. of Amphotericin B over a period of 17 days. Since it was not known how long to continue and since our supply of Amphotericin B was temporarily exhausted, she was sent home.

It is of note that a fasting blood sugar was 106 mg. per cent since many cases of mycoses appear in diabetics.

We later learned that the Amphotericin B this patient had received was probably not sufficient in amount to cure the condition and unfortunately several weeks following discharge the broncho-pleural fistula re-opened and she began to run a fever. A further supply of Amphotericin B was obtained and she was re-admitted to the hospital for its administration. However, at this time examination of the pleural fluid and the sputum were both positive for tubercle bacilli and she was transferred to a tuberculosis sanatorium.

COMMENT

It is probable that the fungus was able to become pathogenic in this patient because of the lowered resistance following the fracture of the hip, the surgery necessary to repair it, and the long convalescence. Blood studies done in the hospital revealed a considerable degree of anemia upon admission which undoubtedly contributed to the lack of resistance. The anemia improved during her hospital stay with proper treatment.

At the time of development of the broncho-pleural fistula, tubercle bacilli were not found in the pleural fluid or in the sputum. The question of whether the large doses of potassium iodide used in the treatment of her mycosis before the Amphotericin B was received was sufficient to soften up the pulmonary fibrosis enough to allow a reactivation of tuberculosis cannot be answered. The re-opening of the broncho-pleural fistula with the presence of tubercle bacilli in the fluid make it possible that this second episode was actually not connected with Aspergillosis and that this actually had been healed. No fungi were found at the time of her second admission to the hospital.

Defervescence of the fever and the closing of the broncho-pleural fistula would seem to testify to the effectiveness of Amphotericin B for the treatment of Aspergillosis, whether the Aspergillus fumagatus was a primary or secondary invader.

Coincidental Occurrence of Bronchial Adenoma and Pulmonary Tuberculosis

A Case Report

ERKKI LAUSTELA, M.D., F.C.C.P.
Helsinki, Finland

Only a few years ago bronchial adenoma was considered a rare tumor. Recently, however, an increasing number of reports have been published of this neoplasm. On the basis of their experience Lindskog and Liebow[3] hold that bronchial adenomata comprise 4 to 5 per cent of all pulmonary neoplasms.

An adenoma originating in the bronchial wall gives rise to symptoms of obstruction, infection and haemorrhage. Similar symptoms are also seen in two diseases which are far more common than adenoma, i.e., carcinoma of the lung and pulmonary tuberculosis. From the point of differential diagnosis the most difficult cases are those in which two diseases clinically resembling each other are coincidently present. The more common disease or the one first diagnosed readily masks the other condition, as is also shown by the case described below.

A carpenter, aged 38, with numerous cases of tuberculosis in the familial history, had a febrile period in the autumn of 1950. After two to three weeks the fever subsided spontaneously. In the following spring the febrile bout recurred and was associated with cough and bloody sputum. Chest x-ray film examination revealed in the right lung a shadow simulating tuberculosis and the patient was sent to a tuberculosis sanatorium with the diagnosis: Tuberculosis pulm. dx. gr. I b. Tubercle bacilli were found for the first time in stained sputum in February 1951. Because of a cavity seen in the right lower lung field, right pneumothorax was instituted in the autumn

FIGURE 1

FIGURE 2

Figure 1: Postero-anterior view of the chest at the time of admission show a roundish shadow in the lower field of the right lung.—*Figure 2:* Bronchogram showing somewhat clumsy and crooked bronchi of the right lower lobe but no contrast medium defects.

From the Thoracic Department of the Surgical Clinic, University of Helsinki.

of 1952 but after six months was discontinued as ineffective. Medical therapy in the sanatorium consisted of streptomycin, PAS and INH. His general physical condition improved, the blood in the sputum disappeared, and he was afebrile nearly the whole time. The cavity in the lower lobe nevertheless persisted and yielded tubercle bacilli in the sputum. He was therefore transferred to the surgical clinic for treatment by resection.

Preoperative routine roentgenograms and tomograms disclosed in the lower field of the right lung a roundish shadow about one inch in diameter, with somewhat diffuse margins. This was considered to be a tuberculoma (Figure 1). In bronchography the bronchi of the right lower lobe were somewhat clumsy and crooked but no contrast medium defects were seen (Figure 2). Bronchoscopy was also attempted but had to be interrupted because of his restlessness and the adenoma was therefore not diagnosed.

Resection of the right lower lobe was performed on February 28, 1957. In the common basal bronchus of the lower lobe, immediately distal to the origin of the bronchus to the apical segment there was a smooth-surfaced tumor nearly one inch in diameter protruding into and narrowing the lumen, and covered by bronchial mucosa of normal appearance. The tumor extended outside the bronchus into lung tissue; about one-third of the neoplasm was situated endobronchially. In the postero-basal segment of the lower lobe there was a tuberculoma about one inch in diameter with indefinite margins, and peripheral to it a thin-walled cavity of nearly the same size.

Microscopic examination showed an adenoma of carcinoid type situated in the bronchial wall and composed of cords of medium-sized pale cells. The partitions between the cords frequently consisted of small capillaries. Cell mitoses were not seen (Figure 3).

Post-operative recovery was normal and he is now receiving further treatment in a sanatorium.

DISCUSSION

In the case reported above a bronchial adenoma was an unexpected finding at a surgical operation performed because of lower lobe tuberculosis with cavity formation. On x-ray film examinations, including bronchography, the presence of an adenoma was not suspected and the

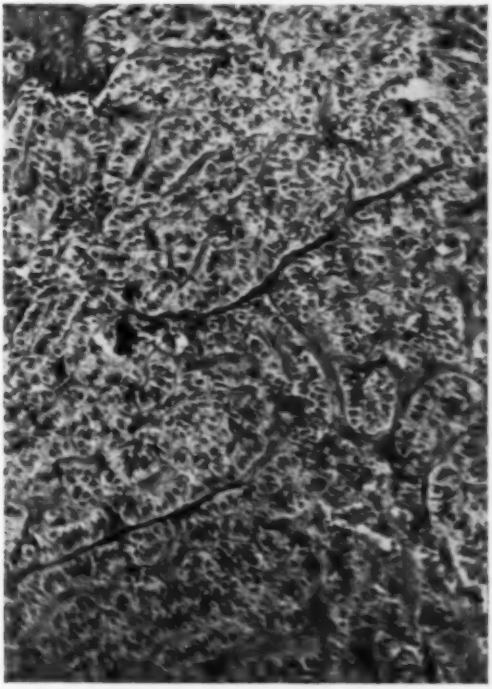

FIGURE 3: Photograph of microscopic section of the bronchial adenoma showing its carcinoid structure. × 250.

roundish shadow was diagnosed as a tuberculoma. The sputum yielded acid-fast bacilli a number of times. The bloody sputum was in no way notably copious or of long duration. The symptoms and examination findings could therefore be fully explained on the base of tuberculosis and no sign pointed to the presence of another disease. Bronchoscopy would undoubtedly have disclosed the tumor but it had to be interrupted. This case warns us to keep in mind that regardless of a confirmed diagnosis of tuberculosis the patients's lung may also be the site of another disease.

The literature contains a number of references to the co-existence of pulmonary tuberculosis and carcinoma of the lung. From Finland, for example, there is a report by Laustela and Thomander.[2] On the other hand, the coincident occurrence of the more rare adenoma and of confirmed tuberculosis has been reported in only two cases in the literature available to us. In the case described by Zorini[4] the patient received the diagnosis of pulmonary tuberculosis on clinical grounds alone and was placed in a sanatorium. There he finally developed actual tuberculosis because, in Zorini's opinion, of his exposure to the disease in the hospital. In the case now under review, acid-fast bacilli were found in the sputa already at an early stage of the disease and the patient's tuberculosis cannot be regarded as consequent upon sanatorium infection. In the case of Aceto and Chakravarty[1] a positive culture for acid-fast bacilli confirmed the diagnosis of pulmonary tuberculosis. Bronchoscopy performed because of atelectasis revealed a bronchial adenoma involving a middle lobe bronchus.

According to Aceto and Chakravarty "the fact that in two thirds of cases of bronchial adenoma the tumor involves the main lower lobe bronchi, while lower lobe tuberculosis as the initial or sole site is relatively uncommon, may be helpful in differentiating this tumor from tuberculosis". In the case here presented, however, the tuberculosis was localized in the lower lobe, which was also the site of the adenoma, rendering differential diagnosis all the more difficult.

Both disease processes in our case thus were situated in the same lobe but had no direct contact with each other. The tuberculosis was localized in the postero-basal segment. The adenoma was situated in the wall of the common basal bronchus, narrowing the lumen but not giving rise to atelectasis. It is possible that impaired ventilation due to the narrowed lumen may have played some role in the development of the tuberculous process.

Lobectomy removed both the main tuberculous focus and the "silent" adenoma since they were situated in the same lobe. In connection with this case there again is reason to emphasize the importance of bronchoscopy in the diagnosis of bronchial adenomata.

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2 Laustela, E. and Thomander, K.: "Co-existence of Bronchial Carcinoma and Pulmonary Tuberculosis," (In Finnish) *Duodecim*, 71:748, 1955.

3 Lindskog, G. E. and Liebow, A. A.: *Thoracic Surgery and Related Pathology*, Appleton-Century-Crofts, Inc., New York, 1953.

4 Zorini, A. O.: "The Clinical Syndrome of the So-called Adenomata," *Dis. Chest*, 25:154, 1954.

Editorial

Operation Bootstrap in Tuberculosis Control in Puerto Rico

The campaign against tuberculosis in Puerto Rico is notable in that it constitutes an example of great achievement in the face of handicaps usually considered insuperable. One of the most densely populated countries in the world, Puerto Rico was, until well past the beginning of the century, one of the poorest. It has no natural resources. Our governor presented a good picture of conditions on the island by asking his listeners to suppose that the population of the entire world were concentrated within the limits of the continental United States with no mines, coal, petroleum, or any other natural resource to support such an enormous population. That supposition, concluded the governor, would give a fairly good idea of the problems faced on this island.

Overcrowding—the huddling of too many persons in a small house, as well as the conglomeration of too many houses within a limited space—is among the problems that make for high tuberculosis mordibity and mortality rates. These conditions still exist in Puerto Rico despite heroic efforts on the part of the insular and federal governments to overcome them.

In 1933, the tuberculosis mortality rate in Puerto Rico was 333 deaths per 100,000 population. In 1957, it was exactly one tenth of the above figure—33 deaths per 100,000. This rate is still high, more than four times as high as that of the continental United States, but for Puerto Rico, it represents a great achievement.

Many articles and several books have been written on the social and economic problems of Puerto Rico since the beginning of the century. Those written before 1940 often pointed out that the efforts to improve health conditions were increasing rather than reducing the problems on the island, since too many people who would have died of communicable diseases were being kept alive by the intense public health campaigns. These articles indicated that this served to worsen the overcrowding and increase the number of mouths to be fed, since the birth rate remained alarmingly high. This point of view has been proved wrong. The health campaigns have been so successful that the death rate of Puerto Rico (7 deaths per 1,000 population in 1957) has been reduced to below that of the continental United States. However, since these health campaigns have been accompanied by enormous and successful efforts to raise the standard of living, especially through the remarkable "Operation Bootstrap" of the Commonwealth government, conditions in Puerto Rico have improved steadily. This is in spite of the fact that more lives are saved from needless death every year and that the population of the island has kept increasing at a rather fast rate.

Puerto Rico has never had a sufficient number of beds for cases of tuberculosis. This has made it necessary for the Health Department to resort to treatment of ambulatory cases in dispensaries, a system that has

great limitations when concerned with a chronic contagious disease like tuberculosis. In 1933, a campaign was started to give ambulatory pneumothorax treatment to as many active cases as possible. This was accompanied by a great case-finding and educational campaign. Later, when streptomycin and PAS became available, they were given free to all active cases. In 1952, distribution of isoniazid in large amounts was initiated and it was given with streptomycin to thousands of cases in dispensaries, for periods ranging from three months to two years or more.

It is difficult to assess the effect this extensive campaign of free treatment may have had on the lowering of the mortality during the last 25 years. Statistics show a steady lowering of the mortality curve since 1944, with a marked drop since 1947, when streptomycin was first used, and an even more noticeable decline since 1952 when the extensive distribution of isoniazid began. In judging these statistics, one has to take into account the enormous strides made in socio-economic progress since the beginning of Operation Bootstrap. Operation Bootstrap has brought new industries, the improvement of housing facilities, higher salaries, better working conditions and the conquest of such debilitating diseases as malaria, uncinariasis, typhoid fever and dysentery.

A recent survey by the United States Public Health Service has shown many flaws in the treatment of ambulatory patients in our public health units. The follow-up of patients is inadequate and there is not proper cooperation between hospitals and dispensaries to permit constant supervision and proper treatment of active cases. The chief of the Bureau of Tuberculosis lacks authority to establish a proper relationship between hospitals and dispensaries, so that a dispensary case needing urgent surgery may not be admitted to the hospital until his condition becomes incurable. Pertinent recommendations were made by the authors of this survey. One of the most important is that all treatments be started in hospitals, and that patients be referred to dispensaries for follow-up after their disease has been controlled. Another recommendation is that a greater use of tuberculin tests and sputum cultures be made in establishing the diagnosis of tuberculosis, and that tuberculin be used routinely as a screening method in case-finding among young children.

BCG vaccine has played no part in the decrease of tuberculosis mortality in Puerto Rico. It was decided, from the beginning of the campaign, that all efforts were to be concentrated on proved methods of tuberculosis control, such as case-finding, education and early treatment of as many cases as possible. We have then, in Puerto Rico, a country where tuberculosis is being controlled by standard methods in spite of extreme over-crowding, great poverty and very limited resources, which proves once more that where there is a will, there is a way.

J. RODRIGUEZ PASTOR, M.D., F.C.C.P.*
Rio Piedras, Puerto Rico

*Clinica Antillas.

The President's Page

THE DOCTOR AND THE HISTORY OF MEDICINE

We are in the middle of one of the greatest periods in medicine, comparable to the beginning of scientific medicine in the Renaissance and the rise of large-scale systematic research at the end of the nineteenth century. If greatness is to be measured by immediate results, it could be asserted that we are in the greatest period, in view of the unparalleled rise in life expectance in the last quarter-century. But much of this achievement has been firmly grounded in the past; to a considerable extent we have been simply the heirs of a fabulous intellectual estate put out at compound interest which has now matured. We are chalking up victories for which the sixteenth century was a preparation and for which the nineteenth established the basis.

But our very victories are perhaps beginning to be destructive to the inheritance. The new problems which we confront perhaps signal a fundamental discontinuity in medical history. In the past, the genuinely progressive medicine was that which merely extended the breadth and precision of the physician's knowledge of his fundamental materials—physiology, pathology, microbiology, and pharmacology. (Medicine in the past concerned itself with other things, too, but often they were blind alleys.) Hence we can see the advance of medical knowledge since the sixteenth century as a progressive expansion. What the doctor borrowed from other disciplines readily became his own because it could be related to what he had already mastered in the subjects which made up the heart of medicine. He was the undisputed master of his domain.

This is changing, and it is a change which threatens the physician's relationship to medicine itself. The nature of the change can best be illustrated by reference to what still remains a very minor part of modern medicine, the use of radioactive materials in the diagnosis and treatment of disease. The physician, with few exceptions, since he cannot be expected to master the complexities of physics, and much less relate physics to traditional medical concepts, finds himself in an essentially new situation. When he makes use of techniques whose principles are outside his sphere of competence, he is at that moment not a doctor at all, in any traditional sense, but a "technician," dependent upon the knowledge of others.

This specific instance is unimportant—no specific instance is. But the place that such foreign and unassimilable techniques assume in medicine is increasing at a very rapid rate, and it is properly a cause for concern. A substantial amount of time in medical school is spent in teaching just such techniques. A great deal of the most advanced research being done today is directed toward the development of techniques for the physician, which, because of the theoretical complexity underlying them, will remain just techniques, fundamentally unrelated to the rest of his medical knowledge. Perhaps most seriously of all, one must look forward to an increased dependence of the physician upon bodies of knowledge which are utterly unmedical, such as engineering of one kind or another.

We must, of course, rejoice at every gain medicine makes in its war against disease, from whatever source it comes (although the dependence of the doctor of the future upon the electronics specialist will be no easy thing to adjust to). But we may also be apprehensive about gains made at the expense of the traditional relationship between the physician and his art. And we do not need to submit supinely to the implications of our techniques.

We can, instead, demand the best of the old along with the new. If there is one eternal lesson that we can learn from our past, it is that the essence of great medicine lies in the unique relationship between doctor and patient. "Medicine," as Osler truly said, "should begin with the patient, continue with the patient, and end with the patient." As long as the physician can maintain this attitude, and assume the responsibilities it implies, his losses to the technicians are negligible.

Which brings us to the point. The obvious way, and perhaps the only way, to insure our connection with the tradition from which modern medicine springs is to know that tradition. This does not mean that there is any value in the collection of historical "facts" to which, one fears, the history of medicine has at times been reduced. That Agricola described the first lung cancer in 1507 or 1509 or whenever is grossly irrelevant to modern medicine. But the

force which drove Agricola to his description is not irrelevant. The history of medicine lives and has meaning when it is studied in sufficient detail to put us into touch with the spirit of the men who shaped it. The techniques of medicine change but the great doctor is recognizable in the 16th or the 20th century. The histories and biographies which can put us into touch with the minds and hearts of our great predecessors can give us a surer sense of our own purpose.

Seymour M. Farber

COMMITTEE ON NOMINATIONS

The Committee on Nominations for the 1960 annual College elections is composed of Dr. Burgess L. Gordon, Albuquerque, New Mexico, Chairman, elected to the committee by the Board of Regents; Dr. George R. Maxwell, Morgantown, West Virginia, elected by the Board of Governors; and Dr. Jack Reiss, Coral Gables, Florida, appointed by the President.

Recommendations for elective offices may be addressed to Dr. Burgess L. Gordon, Chairman, 4902 Constitution Avenue, N.E., Albuquerque, New Mexico. The Committee on Nominations will meet in Dallas, Texas, on November 29, 1959, during the Interim Session of the College.

Chapter News

SOUTHERN CHAPTER

The 16th annual meeting of the Southern Chapter will be held at the Biltmore Hotel, Atlanta, Georgia, November 15 and 16. The following program will be presented:

November 15

8:00 a.m. Registration

9:00 a.m. Diagnostic Session

"Comparative Results in the Use of Two Commercial PPD Skin Tests in 572 Consecutive Admissions"
Benjamin L. Brock, Orlando, Florida

"Difficulties in Diagnosis of Congenital Heart Disease by Catheterization; Observations on Left Heart Blood Labelling Techniques as an Aid"
Albert S. Hyman, New Orleans, Louisiana

"Evaluation of the Chronically Ill Surgical Patient by Tilt Table and Adrenal Responses Correlated with Blood Volumes"
Watts R. Webb and T. V. Stanley, Jr., Jackson, Mississippi

10:45 a.m. Symposium on Bronchogenic Carcinoma

"The X-ray Appearance of Bronchogenic Carcinoma"
John Paul Carter and Emmett R. White,
Chattanooga, Tennessee

"Bronchography, An Invaluable Aid in Distinguishing Unresolved Pneumonia from Bronchogenic Carcinoma"
Sol Katz and Robert Donahoe, Washington, D. C.

"Bronchogenic Carcinoma in Young Men, A Dire Disease"
Howard A. Buechner, New Orleans, Louisiana

"A Broad Palliative Approach to the Patient with Inoperable Bronchogenic Carcinoma"
Joseph Bradford, New Orleans, Louisiana

1:00 p.m. "Clinical Evaluation of the Cyanotic Child"
Willis Hurst, Atlanta, Georgia

"Surgical Perspectives in Cyanotic Heart Disease"
W. C. Sealy, W. Glenn Young, Jr. and Ivan W. Brown, Jr., Durham, North Carolina

"Pulmonary Resection in the First Year of Life"
Donald L. Paulson, Dallas, Texas

"Pulmonary Resection in the Older Patient; Risk vs. Results"
Osler A. Abbott, Atlanta, Georgia

"Dissection of the Aorta; A Great Mimic of Many Diseases"
Thomas W. Mattingly, Washington, D. C.

"Surgical Management of Dissecting Aortic Aneurysms; A Reappraisal"
W. Dean Warren, Charlottesville, Virginia

November 16

9:00 a.m. "Treatment of Essential Hypertension: A Comparative Study of 300 Cases with Five Years' Treatment Preceded by 5-10 Years' Observation"
Frank W. Pickell, Baton Rouge, Louisiana

"Surgical Considerations in the Repair of Atrial Septal Defects"
Richard King, Atlanta, Georgia

"Long-term Results of Medical and Surgical Therapy in Photochromogenic Disease"
David Bahar, Daniel E. Jenkins, Irving Chofnas, and Howard T. Barkley, Houston, Texas

"Changing Concepts in the Therapy of Lung Abscess: A 20-Year Survey"
Mark Wolcott, Oswald H. Coury and George Baum, Coral Gables, Florida

"Tracheal Fenestration—A Useful Adjunct in the Management of Certain Cases of Severe Emphysema"
William K. Swann and Jacob T. Bradshear, Jr., Knoxville, Tennessee

Sixth Annual Paul A. Turner Memorial Lecture—"Myocarditis"
John J. Walsh, New Orleans, Louisiana

CENTRAL INDIA CHAPTER

The Central India Chapter was officially organized by Dr. Raman Viswanathan of New Delhi, Regent of the College, on March 1 in Hyderabad. The following officers were elected at a business meeting held on May 8:

President:	Major K. N. Rao, Hyderabad
1st Vice-President:	Kanwal Chander, Hyderabad
2nd Vice-President:	B. K. Naik, Hyderabad
Secretary-Treasurer:	T. B. Rao, Hyderabad

NEW CHAPTER OFFICERS

EAST PAKISTAN CHAPTER

President:	Abu Khaled Muhammad Abdul Wahed, Dacca
Vice-President:	Nurul Islam, Chittagong
Executive Secretary:	S. A. Altaf Hossain, Dacca
Secretary:	Nazrul Islam, Dacca
Treasurer:	Mohammad Sujaud Dowla, Dacca

PHILIPPINE CHAPTER

President:	Manuel Quisumbing, Sr., San Pablo
President-Elect:	Enrique M. Garcia, Quezon City
Vice-President:	Pacifico D. Nazareno, Manila
Secretary-Treasurer:	Priscilla de Jesus Tablan, Quezon City (re-elected)

REPORT OF THE COMMITTEE ON COLLEGE ESSAY

1959 Prize Essay Contest

This year the Committee on College Essay received 87 requests for information concerning the 1959 Essay Contest. Thirty-one applications were received and 26 essays were submitted from 16 students in the United States and from students in the following countries: Austria (2), Canada (2), Czechoslovakia, England (2), Hungary, Pakistan, and the Philippines. First prize is $500, second prize is $300, and the third prize is $200. All winners also receive certificates of merit.

H. Allan Novack, M.D., Chairman

First Prize

Michael A. Salmon
Middlesex Hospital Medical School, University of London, England
"Pulmonary Hydatidosis, A Review"

Second Prize

L. O. Baum

J. A. Murray

N. H. Oldham

Baylor University College of Medicine, Houston, Texas
"Evaluation of Lung Volumes and Intrapulmonary Gas Mixing in Diseased and Normal Children"

Third Prize (tie)

Rose K. L. Wong
University of Oregon Medical School, Portland, Oregon
"Postoperative Pulmonary Atelectasis"

Jack W. Hall
Medical College of Virginia, Richmond
"Pulmonary Function Tests: Applications, Observations, Interpretations"

1960 Essay Award Contest

The Committee on College Essay is pleased to announce the 1960 contest is now open to undergraduate medical students throughout the world. Three cash awards will again be offered ($500, $300, $200) and essays may be written on any phase of the diagnosis and treatment of chest diseases (cardiovascular or pulmonary). The contest will close on April 1, 1960. Applicants are requested to write to the Executive Offices of the College, 112 East Chestnut Street, Chicago 11, Illinois, for additional information and applications.

SILVER ANNIVERSARY INTERIM SESSION

The Interim Session of the American College of Chest Physicians will be held at the Sheraton Dallas Hotel, Dallas, Texas, on Sunday, November 29 and Monday, November 30, 1959. The American Medical Association will hold its Clinical Meeting in Dallas, December 1 through 4.

College administrative sessions will be held on Sunday, November 29, as listed below:

10:00 a.m.—Executive Council Meeting
12:00 noon—Luncheon
Joint Meeting, Board of Governors and Board of Regents
2:30 p.m.—Semi-Annual Meeting, Board of Regents

A cocktail party and dinner, which will be open to all members of the College, their families, and other interested physicians, will be held on Sunday evening to be followed by the presentation of the *Seventh Charles M. Hendricks Memorial Lecture*. Dr. Orville E. Egbert, El Paso, Texas, will present the Memorial Lecture, which is entitled "Charles Hendricks and the American College of Chest Physicians." Dr. Lawrence M. Shefts, San Antonio, President of the Texas Chapter of the College, will preside and introduce the guest speaker.

Arrangements have been made with Texas Christian University to hold a block of tickets for the football game with Southern Methodist University at Ft. Worth on Saturday, November 28. Sections UF, rows 16, 17 and 18 on the upper deck, on approximately the 25 yard line, are being held for College members. Tickets for the game may be obtained by sending a remittance of $4.00 per ticket, plus 35 cents mailing charge, to:

Ticket Manager, Athletic Department
Texas Christian University
Ft. Worth, Texas

In requesting tickets, please indicate that these seats should be in the section reserved for the American College of Chest Physicians. The game is expected to be sold out in advance and it is therefore necessary that tickets be obtained at once.

Dr. James O. Armstrong, Dallas, is serving as chairman of the arrangements committee for the meeting, and Dr. Robert R. Shaw, Dallas, is chairman of the scientific program committee. The following program will be presented on Monday, November 30:

8:30 a.m.—REGISTRATION

8:55 a.m.—SCIENTIFIC SESSION

Co-Chairmen:
Seymour M. Farber, San Francisco, California
President, American College of Chest Physicians
Robert R. Shaw, Dallas, Texas
Chairman, Scientific Program Committee

9:00 a.m.—*Acute Thoracic Injuries*
Byron H. Evans, Fresno, California

9:30 a.m.—*Esophageal Reconstruction in Infants and Children*
Thomas G. Baffes, Chicago, Illinois

10:00 a.m.—*Congenital Diaphragmatic Hernia in the Adult*
Mark H. Williams, Binghamton, New York

10:30 a.m.—*Pulmonary Resection for Tuberculosis*
Felix Hughes, Memphis, Tennessee

11:00 a.m.—*Open Negative Patients—Long Term Follow-up Studies*
Raymond F. Corpe and Frank A. Blalock, Rome, Georgia

11:30 a.m.—*Spontaneous Pneumothorax in Association with Active Pulmonary Tuberculosis*
Mark M. Ravitch and R. J. Miller, Baltimore, Maryland

12:00 noon—ROUND TABLE LUNCHEONS

1) ***Pulmonary Function***
Maurice S. Segal, Boston, Massachusetts, *Moderator*
Joseph Gordon, Albuquerque, New Mexico
William F. Miller, Dallas, Texas
Jack Reiss, Coral Gables, Florida

2) ***Complications of Cardiac Surgery***
Robert P. Glover, Philadelphia, Pennsylvania, *Moderator*
Thomas G. Baffes, Chicago, Illinois
E. S. Crossett, El Paso, Texas
Johann L. Ehrenhaft, Iowa City, Iowa

3) ***Complications of Pulmonary Resection***
Howard T. Barkley, Houston, Texas, *Moderator*
David J. Dugan, Oakland, California
Byron H. Evans, Fresno, California
Felix Hughes, Memphis, Tennessee

1:55 p.m.—SCIENTIFIC SESSION

Co-Chairmen:

James O. Armstrong, Dallas, Texas
Chairman, General Arrangements Committee

M. Jay Flipse, Miami, Florida
President-Elect, American College of Chest Physicians

2:00 p.m.—*Pleural Mesotheliomas*
Johann L. Ehrenhaft, Iowa City, Iowa

2:30 p.m.—*Alveolar Hyperplasia Following Influenzal Pneumonitis*
John H. Moyer Jr., Kansas City, Missouri

3:00 p.m.—*The Present Status of Surgical Procedures for Patients with Chronic Bronchial Asthma and Chronic Pulmonary Emphysema*
Maurice S. Segal, Boston, Massachusetts

3:30 p.m.—*Acute Pulmonary Histoplasmosis*
Fred E. Tosh, Kansas City, Missouri

4:00 p.m.—*Role of the Left Ventricle in Cardiac Surgery*
Robert P. Glover, Philadelphia, Pennsylvania

4:30 p.m.—*Rupture of Trachea and Bronchi from External Trauma*
William S. Conklin and Stanley F. Bergquist, Portland, Oregon

8:00 p.m.—FIRESIDE CONFERENCES

Hosts:

Members, Texas Chapter, American College of Chest Physicians

Subjects and Discussion Leaders

1) ***Bronchogenic Carcinoma***
Howard T. Barkley, Houston, Texas
Felix Hughes, Memphis, Tennessee

2) ***Problems in Drug Therapy for Pulmonary Tuberculosis***
Howard A. Buechner, New Orleans, Louisiana
Samuel Topperman, Tyler, Texas

3) ***Mycotic Diseases of the Lungs***
Byron H. Evans, Fresno, California
Fred E. Tosh, Kansas City, Kansas

4) ***Pulmonary Emphysema***
Paul L. Richburg, Dallas, Texas
Maurice S. Segal, Boston, Massachusetts

5) ***Open Heart Surgery***
Thomas G. Baffes, Chicago, Illinois
Johann L. Ehrenhaft, Iowa City, Iowa

6) ***Coronary Heart Disease***
George R. Herrmann, Galveston, Texas
Marvin D. Siperstein, Dallas, Texas

7) ***Diaphragmatic Hernia***
Eldon K. Seibel, Dallas, Texas
Mark H. Williams, Binghamton, New York

8) ***Inhalation Therapy***
Albert H. Andrews, Chicago, Illinois
William F. Miller, Dallas, Texas

9) ***Thoracic Injuries***
E. S. Crossett, El Paso, Texas
Lawrence M. Shefts, San Antonio, Texas

10) ***Pleural Effusion—A Diagnostic Problem***
David J. Dugan, Oakland, California
James A. Wier, Denver, Colorado

11) ***Practical Problems with Endoscopy***
Pasquale Ciaglia, Utica, New York
Arthur M. Olsen, Rochester, Minnesota

NOTE: The *Fireside Conferences* are informal and offer an opportunity for free discussion. Discussion leaders will be seated at tables with proper identification. Physicians may participate in the discussions of their choice, or move on to other discussions when and if they choose.

Silver Anniversary Interim Session

AMERICAN COLLEGE OF CHEST PHYSICIANS

Advance Registration

By completing this form and returning it at once to the Executive Offices of the College, you will avoid having to stand in line at the Registration Desk of the Interim Session in Dallas. Your badge and program, as well as luncheon and dinner tickets will be prepared in advance and will be awaiting your arrival at the Sheraton Dallas Hotel.

Please indicate on the coupon below the number of dinner tickets you will require and your first and second choice of the round table luncheons.

Return this form to: American College of Chest Physicians
112 East Chestnut Street
Chicago 11, Illinois

THERE IS NO REGISTRATION FEE

ALL PHYSICIANS ARE CORDIALLY INVITED TO ATTEND

Advance Registration Form

please print

Member..... Non-member.....

Name .....

Address .....

City and State .....

Accompanied by .....

Hotel .....

Arrival date..... Departure date.....

I am enclosing my check in the amount of $..... for reservations as indicated below.

DINNER, SUNDAY, NOVEMBER 29 **$6.00 each**

Please reserve ..... places at the dinner.

ROUND TABLE LUNCHEONS, MONDAY, NOVEMBER 30 **$4.00 each**

1) Pulmonary Function
2) Complications of Cardiac Surgery
3) Complications of Pulmonary Resection

First Choice—No..... Second Choice—No.....

FOOTBALL GAME, SATURDAY, NOVEMBER 28

I have reserved ..... tickets for the football game.

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Announcements

The National Cylinder Gas Division of Chemetron Corporation has been named exclusive distributor for the "Ventalung," a demand-type intermittent positive pressure breathing instrument which is cycled by the patient's own respiration. The unit, developed, by the J. J. Monaghan Company, Inc., Denver, operates with a minimum of patient effort by means of face mask, mouth tube, or tracheotomy. It can be used with either cylinder or piped oxygen supply systems.

The George P. Pilling & Son Company, Philadelphia, has announced a new group of instruments designed for Dr. Chevalier L. Jackson. One of these is a bronchoscopic cord with a new "slip-on" feature that always assures connection and eliminates the troublesome bayonet-type cord. Also introduced recently is a lens front bronchoscopic lamp.

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Thompson PORTABLE MEDI-BREATHER

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PURE AIR DELIVERED TO PATIENT

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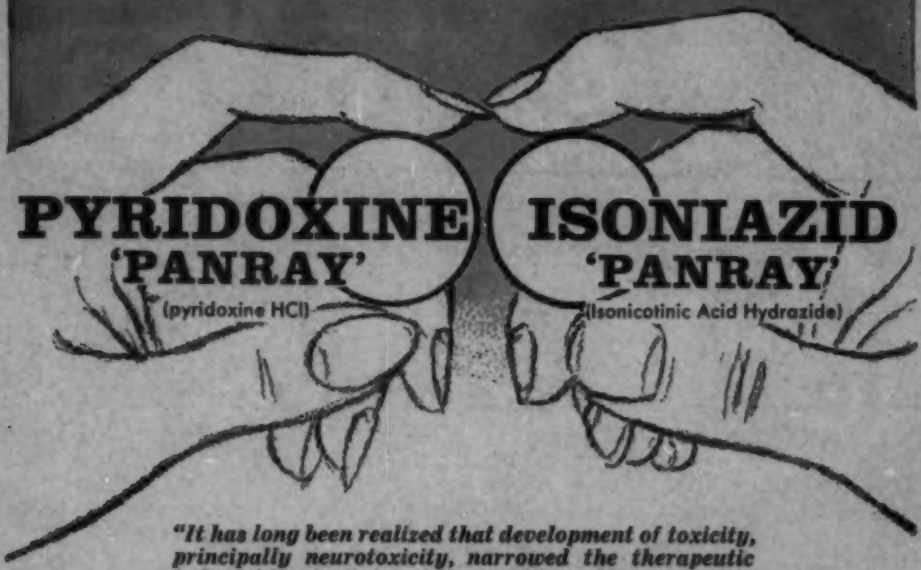

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[1]See View Bulletin 16:52 July '56 Tchertkoff, et al. JAMA 156:1549 (Dec. 25) 1954 Biehl & Viltner Am. Rev. TBc 70:266 Aug. '54 Hughes, et al. N. Eng. J. of Med. 255 23 118:122, 1956 Carlson, et al.